Remarks

Reconsideration of this Application is respectfully requested.

Upon entry of the foregoing amendment, claims 1-14, 22-40 and 47-97 are pending in the application, with1, 47, 48, 51, 57, 64, 66, 73, 76, and 83 being the independent claims. Claims 15-21 and 41-46 are sought to be cancelled without prejudice to or disclaimer of the subject matter therein. New claims 94-97 are sought to be added. Support for the amendment to claims 1, 51, 57, 66, and 76 inserting the term "X^1 is $-S(O)_n-$, wherein n is 0, 1, or 2" is found in the claims as originally filed wherein X^1 was defined to include -S-, -S(O)- and $-S(O)_2-$. Support for the insertion of the variable $R^{9'}$ for the second occurrence of the variable R^9 in claims 1, 51, 53, 57, 61, 66, 70, 76, and 80 is found in the claims as originally filed, where it is clear that the use of the variable R^9 two times was a typographical error. Support for the term "heterocycloalkylene" in claims 49 and 51 can be found in the claims as originally filed. These changes are believed to introduce no new matter, and their entry is respectfully requested.

Based on the above amendment and the following remarks, Applicants respectfully request that the Examiner reconsider all outstanding objections and rejections and that they be withdrawn.

Election/Restriction

Claims 1-5, 35, 49-64, 66-73, 75-83, and 85-93 have been rejected as being an improper Markush grouping. The Examiner is of the opinion that "[t]he recited compounds, while possessing a common utility, present a variable core and, thus, the Markush group represented by the term L in formula I and n in formula A have variably different definitions, rendering the claims clearly improper." (Office Action, page 3).

Applicants respectfully disagree. The claims as amended refer only to compounds of the elected invention. The Examiner refers to non-existent terms L in formula I and n in formula A. In a telephone interview with the Examiner on January 15, 2003, the Examiner indicted that the terms should have been X^1 and A^2. Therefore, Applicants respectfully submit that the Examiner's stated grounds for rejection have been accommodated and the rejection should be withdrawn.

Rejections under 35 U.S.C. § 112, First Paragraph

A. First Rejection (Claims 1-14, 22-40, 47-50, and 52-93)

Claims 1-14, 22-40, 47-50, and 52-93 have been rejected under 35 U.S.C. § 112, first paragraph, as containing subject matter which was not allegedly described in the specification in such a way as to enable one skilled in the art to use the invention. (Office Action, page 3). Applicants respectfully traverse this rejection.

The Examiner is of the opinion that

> [t]he scope of "prodrug" is not adequately enabled. Applicants provide no guidance as how compounds are made more active *in vivo*. The choice of a "prodrug" will vary from drug to drug. Therefore, more than minimal routine experimentation would be required to determine which prodrug will be suitable for the instant invention."

(Office Action, page 3).

Applicants respectfully disagree. The structures of "prodrugs" for the compounds of the invention are defined in the specification at page 33, lines 1-22.

The word "prodrug" is a term of art, well known to one of ordinary skill in the art. The specification provides a definition of prodrugs, provides a list of exemplary compounds that can be used to form prodrugs and provides references discussing the structure and use of prodrugs. Thus, Applicants' use of the word prodrug accords with the word's ordinary meaning and the term is sufficiently described in the specification to enable one of skill in the art to practice the claimed invention. The Examiner indicates that there is no guidance as how compounds are made more active *in vivo*. However, the term prodrug does not necessarily involve compounds being made more active *in vivo*. The only requirement is that the prodrug is converted by metabolic means into a compound of the invention. The Examiner also suggests that more than minimal routine experimentation would be required to determine which prodrug will be suitable for the instant invention. However, the proper standard for enablement is not minimal routine experimentation. An invention can be enabled even if extensive experimentation may be required, as long as the experimentation is not undue. *In re Angstadt*, 190 USPQ 214, 219 (CCPA 1976). Here, the conversion of compounds to prodrugs is well known in the art, and although there may be some experimentation required to determine which prodrugs are more effective then others, the experimentation is all routine. Thus, the claimed invention is enabled.

For the reasons stated above, Applicants respectfully submit that the Examiner has not established a *prima facie* case for the rejection of claims 1-14, 22-40, 47-50, and 52-93 under 35 U.S.C. § 112, first paragraph. Applicants, therefore, respectfully submit that the above rejection has been overcome and should be withdrawn.

B. Second Rejection (Claims 54-56 and 66-88)

Claims 54-56 and 66-88 have been rejected under 35 U.S.C. § 112, first paragraph, as allegedly containing subject matter which was not described in the specification in such a way as to enable one skilled in the art to make and/or use the invention. (Office Action, page 4). Applicants respectfully traverse this rejection.

The Examiner is of the opinion that:

> [t]he scope of the method claims are not adequately enabled solely based on the activity of progesterone provided in the specification. Evidence involving a single compound and two types of cancer was not found sufficient to establish the enablement of claims directed to a method of treating seven types of cancer with members of a class of several compounds *In re Buting* 163 USPQ 689. The remarkable advances in chemotherapy have seen the development of specific compounds to treat specific types of cancer. The great diversity of diseases falling with the "tumor" category means that it is contrary to medical understanding that any agent (let alone a genus of thousands of compounds) could be generally effective against such diseases. The intractability of these disorders is clear evidence that the skill in this art is low relative to the difficulty of the task.
>
> Instant claim language embraces disorders not only for treatment but for prevention which is not remotely enabled. It is presumed in the prevention of the diseases and/or disorders claimed herein there is a way of identifying those people who may develop cancer. There is no evidence of record which would enable the skilled artisan in the

> identification of the people who have the potential of becoming afflicted with the disorders claimed herein.
>
> There never has been a compound capable of treating cancer generally. There are compounds that treat a range of cancers, but no one has ever been able to figure out how to get a compound to treat cancer generally, or even a majority of cancers. Thus, the existence of such a "silver bullet" is contrary to our present understanding in oncology. Even the most broadly effective antitumor agents are only effective against a small fraction of the vast number of different cancers known. This is true in part because cancers arise from a wide variety of sources, such as viruses (e.g., EBV, HHV-8, and HTLV-1), exposure to chemicals such as tobacco tars, genetic disorders, ionizing radiation, and a wide variety of failures of the body's cell growth regulatory mechanisms. Different types of cancers affect different organs and have different methods of growth and harm to the body, and different vulnerabilities. Thus, it is beyond the skill of oncologists today to get an agent to be effective against cancers generally, evidence that the level of skill in this art is low relative to the difficulty of such a task.
>
> Where the utility is unusual or difficult to treat or speculative, the examiner has authority to require evidence that tests relied upon are reasonably predictive of *in vivo* efficacy by those skilled in the art. See *In re Ruskin*, 148 USPQ 221; *Ex part Jovanovics*, 211 USPQ 907; MPEP 2164.05(a).
>
> Patent Protection is granted in return for an enabling disclosure of an invention, not for vague intimations of general ideas that nay or may not be workable. Tossing our the mere germ of an idea does not constitute enabling disclosure. *Genentech Inc. v. Novo Nordisk* 42 USPQ2d 1001.

(Office Action, pages 4-6). Applicants respectfully disagree with the Examiner's analysis and conclusions.

First, claims 66 and 73 have been amended such that the claims do not encompass prevention of cancer. Second, it is now known that cancer cells are, *inter alia*, generally

characterized not only by a loss of cell cycle control but also by resistance to apoptosis. *See generally* Raymond W. Ruddon, *Biochemistry of Cancer, in* Holand-Frei Cancer Medicine, Chapter 2 (Robert C. Blast, Jr., *et al.* eds., 5th ed., B.C. Decker, 2000), a copy of which is attached herewith in a First Supplemental Information Disclosure Statement. Consequently, increasing the rate of apoptosis is recognized by those of skill in the art as an effective method for the treatment of a wide variety of cancers. *See, e.g.*, WO 00/04901, page 3, line 3, through page 5, line 6, a copy of which is submitted in a First Supplemental Information Disclosure Statement. Indeed, caspase activation is recognized, by those of skill in the art of cancer therapy, as a crucial requirement for the sensitivity of tumor cells toward drug-induced cell death. *See, e.g.,* Maret Los, *et al.*, "Cross-Resistance fo CD95- and Drug-Induced Apoptosis as a Consequence of Deficient Activation of Caspases (ICE/Ced-3 Proteases)," *Blood 90*:3118-3129, 3128 (1997), a copy of which has previously been submitted as Document AT9 in an Information Disclosure Statement filed on November 4, 2002. Therefore, it is now recognized by those of skill in the art that agents that increase the rate of apoptosis are effective for the treatment of a wide variety of cancers.

In order for the present claims to be enabled for the treatment of cancer, it is not required that a single compound or even a few compounds be effective against every known type cancer. It is sufficient that the class of compounds as a whole described in the claims has caspase activating activity and that administration of compounds having such activity is capable of treating cancers in general. To the extent that any particular compound within the genus is not effective or that any particular type of cancer does not respond to the administration, these are merely negative embodiments of the claimed invention. As long as the skilled artisan can readily determine which embodiments are negative without undue

experimentation, the invention as a whole is enabled. The examples disclosed in the present specification involving three types of cancer cells and five different compounds of the claimed invention indicate that the compounds are effective in inducing apoptosis in cancer cells. The Examiner has provided no specific evidence to show that this activity is not common to all the compounds encompassed by the invention, that the disclosed examples are not predictive of effective treatment of cancer *in vivo*, or that any cancer would not be sensitive to the induction of apoptosis. In the absence of any such specific evidence showing that the specification is not enabling for the claimed invention, the invention must be considered to be enabled.

For the reasons stated above, Applicants respectfully submit that the evidence submitted herewith is effective to rebut a *prima facie* case for non-enablement of claims 54-56 and 66-88, under 35 U.S.C. § 112, first paragraph, and that the rejection should be withdrawn.

C. Third Rejection (Claims 55, 56, 85, and 86)

Claims 55, 56, 85, and 86 have been rejected under 35 U.S.C. § 112, first paragraph, as allegedly containing subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the art that the inventors, at the time the application was filed, had possession of the claimed invention. (Office Action, page 6). Applicants respectfully traverse this rejection.

The Examiner is of the opinion that:

> [t]he registered trademarks used as reducing agents is not described in the specification. The relationship between a

> trademark and the product it identifies is sometimes indefinite, uncertain, and arbitrary. The formula or characteristics of the product may change from time to time and yet it may continue to be sold under the same trademark. In patent specifications, every element or ingredient of the product should be set forth in positive, exact, intelligible language, so that there will be no uncertainty as to what is meant. See MPEP 608.01(v).

(Office Action, page 6).

Applicants respectfully disagree. Claims 56 and 86 as amended refer to HERCEPTIN and RITUXAN in capital letters and provide the generic name for the drug, as recommended in MPEP 608.01(v). The meanings of both the proprietary and non-proprietary names for each drug are well-known and satisfactorily described in the literature associated with each drug. Thus, the rejection under 35 U.S.C. § 112, first paragraph has been obviated and should be withdrawn.

D. Fourth Rejection (Claims 57-65 and 89-93)

Claims 57-65 and 89-93 have been rejected under 35 U.S.C. § 112, first paragraph, as allegedly containing subject matter which was not described in the specification in such a way as to enable one skilled in the art to make and/or use the invention. (Office Action, page 6). Applicants respectfully traverse this rejection.

The Examiner is of the opinion that:

> [t]he scope of claims 57-65 and 89-93 are not adequately enabled solely based on a disorder responsive to the induction of apoptosis, provided in the specification. Claims 57-65 and 89-93 are the method of treating any and all diseases and/or disorders associated with the induction of apoptosis, which is not remotely enabled. The scope of claims 57-65 and 89-93 includes diseases and/or disorders

> not even known at this time which may be associated with the induction of apoptosis.

(Office action, pages 6-7).

Applicants respectfully disagree. It is well known to those of skill in the art what disorders are responsive to the induction of apoptosis. See, *e.g.*, O'Reilly, *et al. Inflamm. Res.*, *48*:5-21 (1999). O'Reilly states "[a]poptosis has been recognized as an important regulator of tissue development and cellular homeostasis and abnormalities in this process have been implicated as a cause or contributing factor in a broad range of human diseases, including autoimmunity." O'Reilly at 14. This reference was submitted as document AS11 in the Information Disclosure Statement filed on November 4, 2002. See, also, Orrenius, *J. Intern. Med.*, *237*:529-536 (1995). Orrenius states "[f]inally, it has also become increasingly clear that apoptosis plays an important role in a number of diseases, including autoimmune disease, neurodegenerative disease, cancer and HIV/AIDS." Orrenius at 532. This reference was submitted as document AS12 in the Information Disclosure Statement filed on November 4, 2002. Thus, a physician, or one of skill in the art, would be apprized of what diseases or disorders to treat using the present invention based on the level of knowledge in the art and the teachings of the invention.

Further, examples of particular diseases and its symptoms the invention is used to treat can be found in the specification, *inter alia*, at page 35, line 15, through page 36 line 5. Additional diseases are disclosed in the specification at page 38, line 24 through page 41, line 30. Furthermore, methods of treatment are described, *inter alia*, at page 36, line 6 through page 38, line 9 and at page 42, line 1, through page 46, line 10. Finally, the

specification describes the animals intended to be treated with the invention on page 27, lines 13-15.

The Examiner indicates that the claims are not remotely enabled but provides no reasoning to support this conclusion other than the suggestion that there are diseases that are as of yet unknown which may be associated with apoptosis. The specification teaches that disorders responsive to the induction of apoptosis can be treated by the present invention and identifies numerous such diseases. The fact that new diseases discovered in the future may also be responsive to the induction of apoptosis is irrelevant to the enablement of the present invention. The standards for enablement have never been such that inventors must enable embodiments that may be discovered in the future.

Therefore, Applicants respectfully submit the Examiner has not established a *prima facie* case of non-enablement of claims 57-65 and 89-93 under 35 U.S.C. § 112, first paragraph; and Applicants respectfully request that the rejection be withdrawn.

Rejections Under 35 U.S.C. § 112, Second Paragraph

A. First Rejection (Claims 1-14, 22-40, and 47-93)

Claims 1-14, 22-40, and 47-93 have been rejected under 35 U.S.C. § 112, second paragraph, as being indefinite (Office Action, page 7). Applicants respectfully traverse this rejection.

The Examiner is of the opinion that:

> it is not known what is meant by the definition of the substituents on "each ring within A^1 and R^5". It is not known

> whether this is a further definition of A^1 where A^1 contains from 3 to 8 ring atoms and which may be substituted with 1 to 3 groups independently selected form [sic] (C_{1-6})alkyl, cyano, ... in addition to the substituents already defined for A^1.

Applicants respectfully disagree. The definition of A^1 in line 8 of claim 1 as amended refers to a monocyclic or fused polycyclic ring system. The listed substitutions on A^1 may appear in any number on any location of the ring(s). A^1 is further defined in line 19 of the claim to indicate that any ring of the monocyclic or fused polycyclic ring system that contains 3 to 8 ring atoms may comprise 1 to 3 substituents as listed. Thus, the second portion of the claim discussing A^1 merely supplements the first portion of the claim and does not represent a different definition for A^1. Therefore, there is nothing indefinite about the definition of A^1 in claim 1. Independent claims 57, 66, and 76 have been amended in the same fashion.

B. Second Rejection (Claims 1-7, 9, 11, 13, 22-24, 26, 28, 29, 31, 33, 35-37, 39, 49-61, 66-70, 75-80, and 85-93*)*

Claims 1-7, 9, 11, 13, 22-24, 26, 28, 29, 31, 33, 35-37, 39, 49-61, 66-70, 75-80, and 85-93 have been rejected under 35 U.S.C. § 112, second paragraph, as being indefinite (Office Action, page 7). Applicants respectfully traverse this rejection.

The Examiner is of the opinion that the claims "are vague and indefinite in that it is not known what is meant by the two different definitions for the variable R^9."

Applicants respectfully disagree. Claims 1, 51, 53, 57, 61, 66, 70, 76, and 80 as amended refer to variables R^9 and $R^{9'}$. Any confusion over the definition of R^9 has been obviated by the amendment.

C. Third Rejection (Claims 1-14, 22-40, and 47-93)

Claims 1-14, 22-40, and 47-93 have been rejected under 35 U.S.C. § 112, second paragraph, as being indefinite (Office Action, page 7). Applicants respectfully traverse this rejection.

The Examiner is of the opinion that:

> it is not known what is meant by the definition of the substituents on "each ring within A^2 and R^8". It is not known whether this is a further definition of A^2 where A^2 contains from 3 to 8 ring atoms and which may be substituted with 1 to 3 groups independently selected form [sic] (C_{1-6})alkyl, cyano, ... in addition to the substituents already defined for A^2.

Applicants respectfully disagree. The definition of A^2 in line 29 of claim 1 as amended refers to a monocyclic ring system. The listed substitutions on A^2 may appear in any number on any location of the ring. A^2 is further defined in line 39 of the claim to indicate that any ring of the monocyclic ring system that contains 3 to 8 ring atoms may comprise 1 to 3 substituents as listed. Thus, the second portion of the claim discussing A^2 merely supplements the first portion of the claim and does not represent a different definition for A^2. Therefore, there is nothing indefinite about the definition of A^2 in claim 1. Independent claims 49, 51, 57, 66, and 76 have been amended in the same fashion.

D. Fourth Rejection (Claims 1-14, 22-40, and 47-93)

Claims 1-14, 22-40, and 47-93 have been rejected under 35 U.S.C. § 112, second paragraph, as being indefinite (Office Action, page 8). Applicants respectfully traverse this rejection.

The Examiner is of the opinion that:

> it is not known what is meant by the definition of the substituents on "each ring within A^3 and R^{10}". It is not known whether this is a further definition of A^3 where A^3 contains from 3 to 8 ring atoms and which may be substituted with 1 to 3 groups independently selected form [sic] (C_{1-6})alkyl, cyano, ... in addition to the substituents already defined for A^3.

Applicants respectfully disagree. The definition of A^3 in line 49 of claim 1 as amended refers to a monocyclic or fused polycyclic ring system. The listed substitutions on A^3 may appear in any number on any location of the ring(s). A^3 is further defined in line 60 of the claim to indicate that any ring of the monocyclic or fused polycyclic ring system that contains 3 to 8 ring atoms may comprise 1 to 3 substituents as listed. Thus, the second portion of the claim discussing A^3 merely supplements the first portion of the claim and does not represent a different definition for A^3. Therefore, there is nothing indefinite about the definition of A^3 in claim 1. Independent claims 51, 57, 66, and 76 have been amended in the same fashion.

E. Fifth Rejection (Claims 1-14, 22-40, and 47-93)

Claims 1-14, 22-40, and 47-93 have been rejected under 35 U.S.C. § 112, second paragraph, as being indefinite (Office Action, page 8). Applicants respectfully traverse this rejection.

The Examiner is of the opinion that "it is not known what is meant by N-oxide **derivatives**, prodrug **derivatives**, or protected **derivatives**. 'Derivative' implies more than what is positively recited."

Applicants respectfully disagree. The specification clearly defines what is meant by the terms N-oxide derivatives, prodrug derivatives, and protected derivatives. The term N-oxide derivative is defined at page 31, lines 26-28, where it is stated that it is a derivative of a compound of Formula I in which nitrogens are in an oxidized state (*i.e.*, O-N) and which possess the desired pharmacological activity. It is clear what is encompassed by this definition as it only encompasses compounds of Formula I in which the nitrogens are oxidized. The term prodrug derivative is defined at page 33, lines 1–22, where it is stated that a prodrug is a compound which is convertible *in vivo* by metabolic means to a compound of the invention. It is clear what is encompassed by this definition as it only encompasses claimed compounds in which one or more reactive sites are derivatized with a moiety that is removed *in vivo* by metabolic means. Similarly, the term protected derivative is clearly defined in the specification at page 33, lines 23-29, where it is stated that it is a derivative of compounds of the invention in which a reactive site or sites are blocked with protecting groups. It is clear what is encompassed by this definition as it only encompasses claimed compounds in which one or more reactive sites are blocked with

protecting groups. Thus, the term derivative as used here is clearly defined by the specification.

F. Sixth Rejection (Claims 1, 57-59, 66-68, and 76-78)

Claims 1, 57-59, 66-68, and 76-78 have been rejected under 35 U.S.C. § 112, second paragraph, as being indefinite (Office Action, page 8). Applicants respectfully traverse this rejection.

The Examiner is of the opinion that the claims "recite the limitation '**4-hydroxy-6-methyl-2-oxo**-2H-pyran-3-yl' in structure of Formula II(a). There is insufficient antecedent basis for this limitation in the claim."

Applicants respectfully disagree. Claims 1, 57, 66, and 76 as amended clarify that any ring in A^1 having 3 to 8 ring atoms may be substituted with 1 to 3 groups independently selected from a group comprising hydroxy, methyl, and oxo groups. Thus, there is proper antecedent basis for this limitation in the claims.

G. Seventh Rejection (Claim 1)

Claim 1 has been rejected under 35 U.S.C. § 112, second paragraph, as being indefinite (Office Action, page 8). Applicants respectfully traverse this rejection.

The Examiner is of the opinion that the claim "recites the limitation 'mono-substituted by fluoro, bromo, iodo, nitro, methyl, isopropyl, ethoxy or methylsulfanyl' in the

proviso with respect to the definition of A^3. There is insufficient antecedent basis for this limitation in the claim."

Applicants respectfully disagree. Claim 1 as amended clarifies that any ring in A^3 having 3 to 8 ring atoms may be substituted with 1 to 3 groups independently selected from a group comprising halo, nitro, (C_{1-6})alkyl, alkoxy, and alkylsulfanyl groups. Thus, there is proper antecedent basis for this limitation in the claim.

H. Eighth Rejection (Claim 1)

Claim 1 has been rejected under 35 U.S.C. § 112, second paragraph, as being indefinite (Office Action, page 8). Applicants respectfully traverse this rejection.

The Examiner is of the opinion that the claim "recites the limitation 'substituted by at least one of chloro, hydroxy or methoxy' in the proviso with respect to the definition of A^3. There is insufficient antecedent basis for this limitation in the claim."

Applicants respectfully disagree. Claim 1 as amended clarifies that any ring in A^3 having 3 to 8 ring atoms may be substituted with 1 to 3 groups independently selected from a group comprising halo, hydroxy, and alkoxy groups. Thus, there is proper antecedent basis for this limitation in the claim.

I. Ninth Rejection (Claim 2)

Claim 2 has been rejected under 35 U.S.C. § 112, second paragraph, as being indefinite (Office Action, page 9). Applicants respectfully traverse this rejection.

The Examiner is of the opinion that the claim "recites the limitation 'substituted by at least one of halogen, nitro, hydroxy (C_{1-6})alkyl, methoxy, ethoxy and methylsulfanyl' in proviso with respect to the definition of A^3. There is insufficient antecedent basis for this limitation in the claim."

Applicants respectfully disagree. Claim 1 as amended, from which claim 2 depends, clarifies that any ring in A^3 having 3 to 8 ring atoms may be substituted with 1 to 3 groups independently selected from a group comprising halo, nitro, hydroxy, (C_{1-6})alkyl, alkoxy, and alkylsulfanyl groups. Thus, there is proper antecedent basis for this limitation in the claim.

J. Tenth Rejection (Claim 2)

Claim 2 has been rejected under 35 U.S.C. § 112, second paragraph, as being indefinite (Office Action, page 9). Applicants respectfully traverse this rejection.

The Examiner is of the opinion that the claim "recites the limitation 'halogen and (C_{1-6})alkyl' in proviso with respect to the definition of A^3. There is insufficient antecedent basis for this limitation in the claim."

Applicants respectfully disagree. Claim 1 as amended, from which claim 2 depends, clarifies that any ring in A^3 having 3 to 8 ring atoms may be substituted with 1 to 3 groups independently selected from a group comprising halo and (C_{1-6})alkyl groups. Thus, there is proper antecedent basis for this limitation in the claim.

K. Eleventh Rejection (Claim 3)

Claim 3 has been rejected under 35 U.S.C. § 112, second paragraph, as being indefinite (Office Action, page 9). Applicants respectfully traverse this rejection.

The Examiner is of the opinion that the claim "recites the limitation '**4-hydroxy-6-methyl-2-oxo**-2H-pyran-3-yl' in the proviso. There is insufficient antecedent basis for this limitation in the claim."

Applicants respectfully disagree. Claim 1 as amended, from which claim 3 depends, clarifies that any ring in A^1 having 3 to 8 ring atoms may be substituted with 1 to 3 groups independently selected from a group comprising hydroxy, methyl, and oxo groups. Thus, there is proper antecedent basis for this limitation in the claim.

L. Twelfth Rejection (Claims 7, 24, 29, 37, and 39)

Claims 7, 24, 29, 37, and 39 have been rejected under 35 U.S.C. § 112, second paragraph, as being indefinite (Office Action, page 9). Applicants respectfully traverse this rejection.

The Examiner is of the opinion that the claims "recite the limitation '**4-hydroxy-6-methyl-2-oxo**-2H-pyran-3-yl or **4-methoxy-6-methyl-2-oxo**-2H-pyran-3-yl' in the definition of A^1. There is insufficient antecedent basis for this limitation in the claim."

Applicants respectfully disagree. Claim 1 as amended, from which claims 7, 24, 29, 37, and 39 depend, clarifies that any ring in A^1 having 3 to 8 ring atoms may be substituted

with 1 to 3 groups independently selected from a group comprising hydroxy, alkyl, and alkoxy groups. Thus, there is proper antecedent basis for this limitation in the claims.

M. Thirteenth Rejection (Claims 9 and 31)

Claims 9 and 31 have been rejected under 35 U.S.C. § 112, second paragraph, as being indefinite (Office Action, page 9). Applicants respectfully traverse this rejection.

The Examiner is of the opinion that the claims "recite the limitation '**4-hydroxy-6-methyl-2-oxo**-5,6-dihydro-2H-pyran-3-yl or **4-methoxy-6-methyl-2-oxo**-5,6-dihydro-2H-pyran-3-yl' in the definition of A^1. There is insufficient antecedent basis for this limitation in the claim."

Applicants respectfully disagree. Claim 1 as amended, from which claims 9 and 31 depend, clarifies that any ring in A^1 having 3 to 8 ring atoms may be substituted with 1 to 3 groups independently selected from a group comprising hydroxy, alkyl, and oxo groups. Thus, there is proper antecedent basis for this limitation in the claims.

N. Fourteenth Rejection (Claims 11 and 33)

Claims 11 and 33 have been rejected under 35 U.S.C. § 112, second paragraph, as being indefinite (Office Action, page 9). Applicants respectfully traverse this rejection.

The Examiner is of the opinion that the claims "recite the limitation '**2-hydroxy-6-oxo**-cyclohex-1-yl or **2-methoxy-6-oxo**–cyclohex-1-yl' in the definition of A^1. There is insufficient antecedent basis for this limitation in the claim."

Applicants respectfully disagree. Claim 1 as amended, from which claims 11 and 33 depend, clarifies that any ring in A^1 having 3 to 8 ring atoms may be substituted with 1 to 3 groups independently selected from a group comprising hydroxy, alkoxy, and oxo groups. Thus, there is proper antecedent basis for this limitation in the claims.

O. Fifteenth Rejection (Claim 13)

Claim 13 has been rejected under 35 U.S.C. § 112, second paragraph, as being indefinite (Office Action, page 10). Applicants respectfully traverse this rejection.

The Examiner is of the opinion that the claim "recites the limitation '**R^{11} substituted 4-hydroxy-2-oxo**-quinolinyl or **4-methoxy-2-oxo**-quinolinyl' in the definition of A^1. There is insufficient antecedent basis for this limitation in the claim."

Applicants respectfully disagree. Claim 1 as amended, from which claim 13 ultimately depends, clarifies that any ring in A^1 having 3 to 8 ring atoms may be substituted with 1 to 3 groups independently selected from a group comprising hydroxy, oxo, and alkoxy groups. Thus, there is proper antecedent basis for this limitation in the claim.

P. Sixteenth Rejection (Claim 14)

Claim 14 has been rejected under 35 U.S.C. § 112, second paragraph, as being indefinite (Office Action, page 10). Applicants respectfully traverse this rejection.

The Examiner is of the opinion that the claim is vague and indefinite "in that the nomenclature is missing an open parenthesis."

Claim 14 has been amended to insert the missing parenthesis. Therefore, the basis for this rejection has been accomodated.

Q. Seventeenth Rejection (Claim 35)

Claim 35 has been rejected under 35 U.S.C. § 112, second paragraph, as being indefinite (Office Action, page 10). Applicants respectfully traverse this rejection.

The Examiner is of the opinion that the claim "recites the limitation 'n' in the compound of Formula I(G). There is insufficient antecedent basis for this limitation in the claim."

Applicants respectfully disagree. Claim 1 as amended, from which claim 35 depends, recites "$S(O)_n$". Thus, there is proper antecedent basis for this limitation in the claim.

R. Eighteenth Rejection (Claims 35 and 36)

Claims 35 and 36 have been rejected under 35 U.S.C. § 112, second paragraph, as being indefinite (Office Action, page 10). Applicants respectfully traverse this rejection.

The Examiner is of the opinion that the claims "are vague and indefinite in that it is not known what is meant by the definition of n which is as defined in claim 1."

Applicants respectfully disagree. Claim 1 as amended, from which claim 35 depends, includes a definition of n. Thus, there is proper antecedent basis for this limitation in the claims.

S. Nineteenth Rejection (Claims 36-40)

Claims 36-40 have been rejected under 35 U.S.C. § 112, second paragraph, as being indefinite (Office Action, page 10). Applicants respectfully traverse this rejection.

The Examiner is of the opinion that the claims "recite the limitation 'n' in the compound of Formula (1). There is insufficient antecedent basis for this limitation in the claim."

Applicants respectfully disagree. Claim 1 as amended, from which claims 36-40 ultimately depend, recites "$S(O)_n$". Thus, there is proper antecedent basis for this limitation in the claims.

T. Twentieth Rejection (Claim 48)

Claim 48 has been rejected under 35 U.S.C. § 112, second paragraph, as being indefinite (Office Action, page 10). Applicants respectfully traverse this rejection.

The Examiner is of the opinion that the claim "is vague and indefinite as it is not known what is meant by the second period at the end of the claim."

Claim 48 has been amended to deleted the second period. Therefore, the basis for this rejection has been accommodated.

U. Twenty-first Rejection (Claims 49, 60, 69, and 79)

Claims 49, 60, 69, and 79 have been rejected under 35 U.S.C. § 112, second paragraph, as being indefinite (Office Action, page 10). Applicants respectfully traverse this rejection.

The Examiner is of the opinion that the claims "recite the limitation 'substituted pyran, quinoline, cyclohexenyl and phenyl' in the definition of A^1. There is insufficient antecedent basis for this limitation in the claim."

Applicants respectfully disagree. Claims 1, 57, 66, and 76 as amended, from which claims 49, 60, 69, and 79 depend, respectively, define A^1 as a monocyclic or fused polycyclic ring system selected from aryl containing a total of 6 to 14 ring atoms, heteroaryl containing a total of 5 to 14 ring atoms and unsaturated, partially unsaturated or saturated carbocycloalkyl or heterocycloalkyl each containing a total of 3 to 14 ring atoms. This definition clearly encompasses pyran, quinoline, cyclohexenyl and phenyl. Thus, there is proper antecedent basis for this limitation in the claims.

V. Twenty-second Rejection (Claims 49 and 51)

Claims 49 and 51 have been rejected under 35 U.S.C. § 112, second paragraph, as being indefinite (Office Action, page 10). Applicants respectfully traverse this rejection.

The Examiner is of the opinion that the claims "recite the limitation 'heteroalkylene' in the definition of R^6. There is insufficient antecedent basis for this limitation in the claim."

Applicants respectfully disagree. Claims 49 and 51 have been amended to recite heterocycloalkylene rather than heteroalkylene. Thus, there is proper antecedent basis for this limitation in the claims.

W. Twenty-third Rejection (Claims 52, 60, 69, and 79)

Claims 52, 60, 69, and 79 have been rejected under 35 U.S.C. § 112, second paragraph, as being indefinite (Office Action, page 10). Applicants respectfully traverse this rejection.

The Examiner is of the opinion that the claims "recite the limitation 'n' in the compound of Formula (1). There is insufficient antecedent basis for this limitation in the claim."

Applicants respectfully disagree. Claims 1, 57, 66, and 76 as amended, from which claims 49, 60, 69, and 79 depend, respectively, recite "$S(O)_n$". Thus, there is proper antecedent basis for this limitation in the claims.

X. Twenty-fourth Rejection (Claims 52-56)

Claims 52-56 have been rejected under 35 U.S.C. § 112, second paragraph, as being indefinite (Office Action, page 11). Applicants respectfully traverse this rejection.

The Examiner is of the opinion that the claims "recite the limitation 'prodrug' in the compound of Formula II. There is insufficient antecedent basis for this limitation in the claim."

Applicants respectfully disagree. Claim 51, from which claims 52-56 depend, recites the term "prodrug" in line 50. Thus, there is proper antecedent basis for this limitation in the claims.

Y. Twenty-fifth Rejection (Claims 57, 66, and 76)

Claims 57, 66, and 76 have been rejected under 35 U.S.C. § 112, second paragraph, as being indefinite (Office Action, page 11). Applicants respectfully traverse this rejection.

The Examiner is of the opinion that the claims "recite the limitation 'mono-substituted by bromo, hydroxy, methyl, or isopropyl' in the proviso with respect to the definition of A^3. There is insufficient antecedent basis for this limitation in the claim."

Applicants respectfully disagree. Claims 57, 66, and 76 as amended clarify that any ring in A^3 having 3 to 8 ring atoms may be substituted with 1 to 3 groups independently selected from a group comprising halo, hydroxy, and (C_{1-6})alkyl groups. Thus, there is proper antecedent basis for this limitation in the claims.

Z. Twenty-sixth Rejection (Claims 57, 58, 66, 67, 76, and 77)

Claims 57, 58, 66, 67, 76, and 77 have been rejected under 35 U.S.C. § 112, second paragraph, as being indefinite (Office Action, page 11). Applicants respectfully traverse this rejection.

The Examiner is of the opinion that the claims "recite the limitation 'substituted by at least one of Cl and methoxy and not substituted by methylsulfanyl, amino, methylamino

and dimethylamino' in proviso with respect to the definition of A^3. There is insufficient antecedent basis for this limitation in the claim."

Applicants respectfully disagree. Claims 57, 66, and 76 as amended clarify that any ring in A^3 having 3 to 8 ring atoms may be substituted with 1 to 3 groups independently selected from a group comprising halo, alkoxy, amino, alkylamino, and alkylsulfanyl. It is proper to limit claims to a subset of a disclosed Markush group such as is present in the claims. Thus, there is proper antecedent basis for this limitation in the claims.

AA. Twenty-seventh Rejection (Claims 58, 67, and 77)

Claims 58, 67, and 77 have been rejected under 35 U.S.C. § 112, second paragraph, as being indefinite (Office Action, page 11). Applicants respectfully traverse this rejection.

The Examiner is of the opinion that the claims "recite the limitation 'mono-substituted by bromo, nitro, hydroxy, methyl, or isopropyl' in the proviso with respect to the definition of A^3. There is insufficient antecedent basis for this limitation in the claim."

Applicants respectfully disagree. Claims 57, 66, and 76 as amended, from which claims 58, 67, and 77 depend, respectively, clarify that any ring in A^3 having 3 to 8 ring atoms may be substituted with 1 to 3 groups independently selected from a group comprising halo, nitro, hydroxy, and (C_{1-6})alkyl groups. Thus, there is proper antecedent basis for this limitation in the claims.

AB. Twenty-eighth Rejection (Claims 58, 59, 67, 68, 77, and 78)

Claims 58, 59, 67, 68, 77, and 78 have been rejected under 35 U.S.C. § 112, second paragraph, as being indefinite (Office Action, page 11). Applicants respectfully traverse this rejection.

The Examiner is of the opinion that the claim "recite the limitation ' nitro' in the proviso with respect to the definition of A^3. There is insufficient antecedent basis for this limitation in the claim."

Applicants respectfully disagree. Claims 57, 66, and 76 as amended, from which claims 58, 59, 67, 68, 77, and 78 depend, respectively, clarify that any ring in A^3 having 3 to 8 ring atoms may be substituted with 1 to 3 groups independently selected from a group comprising nitro. Thus, there is proper antecedent basis for this limitation in the claims.

AC. Twenty-ninth Rejection (Claims 59, 68, and 78)

Claims 59, 68, and 78 have been rejected under 35 U.S.C. § 112, second paragraph, as being indefinite (Office Action, page 11). Applicants respectfully traverse this rejection.

The Examiner is of the opinion that the claims "recite the limitation 'substituted by at least one of bromo, chloro, hydroxy, nitro, methoxy and (C_{1-3})alkyl' in the proviso with respect to the definition of A^3. There is insufficient antecedent basis for this limitation in the claim."

Applicants respectfully disagree. Claims 57, 66, and 76 as amended, from which claims 59, 68, and 78 depend, respectively, clarify that any ring in A^3 having 3 to 8 ring

atoms may be substituted with 1 to 3 groups independently selected from a group comprising halo, hydroxy, nitro, alkoxy, and (C_{1-6})alkyl. Thus, there is proper antecedent basis for this limitation in the claims.

AD. Thirtieth Rejection (Claims 59, 68, and 78)

Claims 59, 68, and 78 have been rejected under 35 U.S.C. § 112, second paragraph, as being indefinite (Office Action, page 12). Applicants respectfully traverse this rejection.

The Examiner is of the opinion that the claims "recite the limitation '(C_{1-3})alkyl' in proviso with respect to the definition of A^3. There is insufficient antecedent basis for this limitation in the claim."

Applicants respectfully disagree. Claims 59, 68, and 78 have been amended to recite (C_{1-6})alkyl. Claims 57, 66, and 76 as amended, from which claims 59, 68, and 78 depend, respectively, clarify that any ring in A^3 having 3 to 8 ring atoms may be substituted with 1 to 3 groups independently selected from a group comprising (C_{1-6})alkyl. Thus, there is proper antecedent basis for this limitation in the claims.

AE. Thirty-first Rejection (Claims 63, 72, and 82)

Claims 63, 72, and 82 have been rejected under 35 U.S.C. § 112, second paragraph, as being indefinite (Office Action, page 12). Applicants respectfully traverse this rejection.

The Examiner is of the opinion that the claims "are vague and indefinite in that it is not known what is meant by thiazepan in the third species on page 130 and 143, respectively. There is insufficient antecedent basis for this limitation in the claim."

Claims 63, 72, and 82 have amended to recite thiazepin rather than thiazepan. Thus, there is proper antecedent basis for this limitation in the claims.

AF. Thirty-second Rejection (Claims 63, 72, and 82)

Claims 63, 72, and 82 have been rejected under 35 U.S.C. § 112, second paragraph, as being indefinite (Office Action, page 12). Applicants respectfully traverse this rejection.

The Examiner is of the opinion that the claims are vague and indefinite "in that the nomenclature of the species spanning lines 15-16 on page 132 and 145 and lines 25-26 on page 158, respectively are missing an open parenthesis."

Claims 63, 72, and 82 have been amended to insert the missing parentheses. Therefore, the basis for this rejection has been accommodated.

AG. Thirty-third Rejection (Claims 57-65 and 89-93)

Claims 57-65 and 89-93 have been rejected under 35 U.S.C. § 112, second paragraph, as being indefinite (Office Action, page 12). Applicants respectfully traverse this rejection.

The Examiner is of the opinion that the claims are vague and indefinite "in that the claim provides for the use of claimed compounds, but the claim does not set forth any steps involved in determining which are responsive to the induction of apoptosis."

Applicants respectfully disagree. The test for indefiniteness is whether one skilled in the art would understand the bounds of the claims when read in light of the specification. If the claims read in light of the specification reasonably apprise those skilled in the art of the scope of the invention, § 112 demands no more. The degree of precision necessary for adequate claims is a function of the nature of the subject matter. *Miles Lab., Inc. v. Shandon, Inc.*, 27 U.S.P.Q.2d 1123, 1126 (Fed. Cir. 1993) (citations omitted).

As discussed above, disorders responsive to the induction of apoptosis are well known in the art. Thus, a physician, or one of skill in the art, would be apprized of what diseases or disorders to treat using the present invention based on the level of knowledge in the art and the teachings of the invention.

Further, examples of particular diseases and its symptoms the invention is used to treat can be found in the specification, *inter alia*, at page 35, line 15, through page 36 line 5. Additional diseases are disclosed in the specification at page 38, line 24 through page 41, line 30. Furthermore, methods of treatment are described, *inter alia*, at page 36, line 6 through page 38, line 9 and at page 42, line 1, through page 46, line 10. Finally, the specification describes the animals intended to be treated with the invention on page 27, lines 13-15.

In addition, claims 57-65 and 89-93 recite an active positive step on how to practice the invention. Independent method claim 57 states "A method of treating a disorder responsive to the induction of apoptosis . . .comprising administering to a mammal in need

of such treatment an effective amount of a compound of Formula I." The language used in this claim teaches one of skill in the art how to practice the invention, namely, by administering an effective amount of a compound.

Therefore, Applicants respectfully submit the Examiner has not established a *prima facie* case of indefiniteness under 35 U.S.C. § 112, second paragraph; and Applicants respectfully request that the rejection be withdrawn.

AH. Thirty-fourth Rejection (Claim 75)

Claim 75 has been rejected under 35 U.S.C. § 112, second paragraph, as being indefinite (Office Action, page 15). Applicants respectfully traverse this rejection.

The Examiner is of the opinion that the claim "is vague and indefinite in that it is not known what is meant by 'skin cancer an prostatic carcinoma' in the last line of the claim."

Claim 75 has been amended to recite "skin cancer and prostatic carcinoma." Therefore, the basis for this rejection has been accommodated.

AI. Thirty-fifth Rejection (Claim 78)

Claim 78 has been rejected under 35 U.S.C. § 112, second paragraph, as being indefinite (Office Action, page 15). Applicants respectfully traverse this rejection.

The Examiner is of the opinion that the claim "is vague and indefinite in that it is not known what is meant by (C_{1-3})alky."

Claim 78 has been amended to recite "(C_{1-6})alkyl." Therefore, the basis for this rejection has been accommodated.

Applicants respectfully submit that all of the stated grounds for the rejection of claims 1-14, 22-40, and 47-93 under 35 U.S.C. § 112, second paragraph, have been traversed, accommodated or rendered moot. Therefore, Applicants respectfully submit that this rejection should be withdrawn.

Rejections Under 35 U.S.C. § 102

Claims 1-7, 9, 11, 13, 22-24, 26, 28, 29, 31, 33, 35-37, 39, 49-61, 66-70, 75-80, and 85-93 were rejected under 35 U.S.C. § 102(a) as being anticipated by Stockwell *et al.* (WO 00/07017). (Office Action, page 15). Applicants respectfully traverse this rejection.

The Examiner is of the opinion that "Stockwell teaches the compounds of the instant invention as shown in the CAPLUS printout herein provided."

Applicants respectfully disagree. All of the compounds disclosed in the CAPLUS printout are specifically excluded by the present claims. Each compound corresponds to Formula II(a) of the present invention. The claims specifically exclude compounds of Formula II(a) in which A^3 is phenyl substituted by at least one of chloro, hydroxy or methoxy. This exclusion encompasses the first 14 compounds disclosed in the CAPLUS printout (RN 257292-28-7, 257292-29-8, 257292-30-1, 257292-31-2, 257292-32-3, 257292-33-4, 257292-34-5, 257292-35-6, 257292-36-7, 257292-37-8, 257292-38-9, 257292-39-0, 257292-40-3, and 257292-41-4). The claims also specifically exclude compounds of Formula II(a) in which A^3 is phenyl which is mono-substituted by fluoro, bromo, iodo, nitro, methyl,

isopropyl, ethoxy, or methylsulfanyl. This exclusion encompasses the last three compounds disclosed in the CAPLUS printout (RN 257292-42-5, 257292-43-6, and 257292-44-7). As all of the compounds disclosed in the CAPLUS printout are specifically excluded by the present claims, Stockwell *et al.* cannot anticipate the claims. Therefore, Applicants respectfully submit that this rejection should be withdrawn.

Claim Objections

Claims 5, 6, 22, 28, 36, and claims dependent thereon have been objected to under 37 C.F.R. 1.75(c) as being in improper form because a multiple dependent claim must be in the alternative. (Office Action, page 15). Applicants respectfully traverse.

Claims 5, 6, 22, 28, and 36 have been amended to be dependent from a single claim. Therefore, Applicants respectfully submit that this objection should be withdrawn.

Conclusion

All of the stated grounds of objection and rejection have been properly traversed, accommodated, or rendered moot. Applicants therefore respectfully request that the Examiner reconsider all presently outstanding objections and rejections and that they be withdrawn. Applicants believe that a full and complete reply has been made to the outstanding Office Action and, as such, the present application is in condition for allowance. If the Examiner believes, for any reason, that personal communication will expedite

prosecution of this application, the Examiner is invited to telephone the undersigned at the number provided.

Prompt and favorable consideration of this Amendment and Reply is respectfully requested.

Respectfully submitted,

STERNE, KESSLER, GOLDSTEIN & FOX P.L.L.C.

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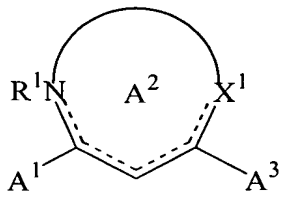
Version with markings to show changes made

Claims 15-21 and 41-46 were canceled without prejudice or disclaimer.

Claims 1, 5, 6, 14, 22, 28, 36, 48-53, 56-61, 63, 66-70, 72, 73, 75-80, 82, and 86 were amended as follows.

1. (once amended) A compound of Formula I:



I

in which:

the dashed lines indicate optional unsaturation without violating valency rules;

R^1 is hydrogen, (C_{1-6})alkyl or $-C(O)R^6$, wherein R^6 is as defined below, or R^1 is absent when a double bond exists between the nitrogen atom to which R^1 is attached and an adjacent ring atom or R^1 is as defined below;

X^1 is <u>$-S(O)_n-$, wherein n is 0, 1, or 2</u> [$-NR^2-$, -S-, -S(O)-, $-S(O)_2-$ or -O-, wherein R^2 is hydrogen or (C_{1-6})alkyl or is absent when a double bond exists between the nitrogen atom to which R^2 is attached and an adjacent ring atom];

A^1 is a monocyclic or fused polycyclic ring system selected from aryl containing a total of 6 to 14 ring atoms, heteroaryl containing a total of 5 to 14 ring atoms and unsaturated, partially unsaturated or saturated carbocycloalkyl or heterocycloalkyl each containing a total of 3 to 14 ring atoms, [or A^1 together with R^1 and the atoms to which A^1 and R^1 are attached forms a fused polycyclic ring system selected from heteroaryl and unsaturated, partially unsaturated or saturated heterocycloalkyl in any case containing a total of 10 to 15 ring atoms,] wherein A^1 may be substituted with a group selected from $-X^2R^3$, $-X^2OR^3$, $-X^2C(O)R^3$, $-X^2OC(O)R^3$, $-X^2C(O)OR^3$, $-X^2SR^3$, $-X^2S(O)R^3$, $-X^2S(O)_2R^3$, $-X^2NR^3R^4$, $-X^2NR^4C(O)R^3$, $-X^2NR^4C(O)OR^3$, $-X^2C(O)NR^3R^4$, $-X^2NR^4C(O)NR^3R^4$,

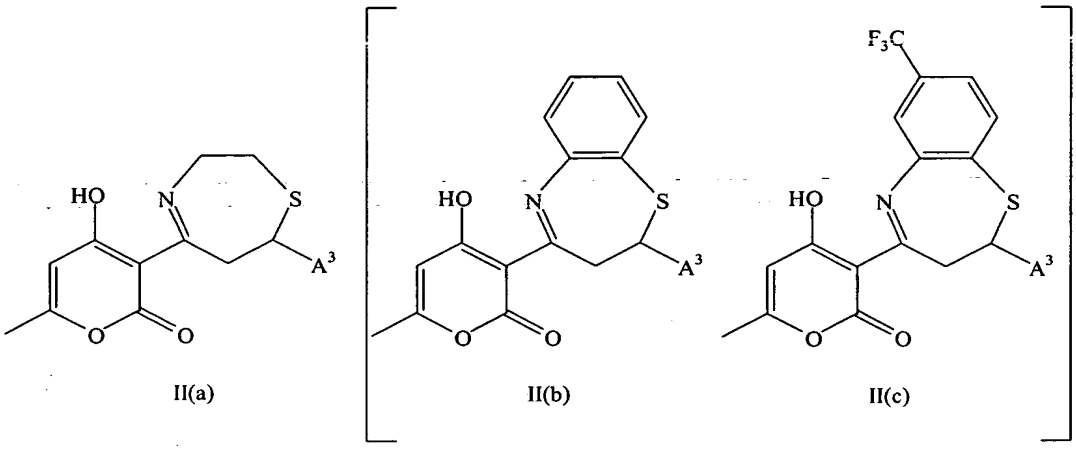
$-X^2NR^4C(NR^4)NR^3R^4$, $-X^2NR^4S(O)_2R^3$ and $-X^2S(O)_2NR^3R^4$, wherein X^2 is a bond or (C_{1-6})alkylene, R^3 is $-X^2R^5$ wherein X^2 is as defined above and R^5 is aryl containing a total of 6 to 10 ring atoms, heteroaryl containing a total of 5 to 10 ring atoms or unsaturated, partially unsaturated or saturated carbocycloalkyl or heterocycloalkyl each containing a total of 3 to 10 ring atoms, and R^4 at each occurrence independently is hydrogen, (C_{1-6})alkyl or halo-substituted (C_{1-6})alkyl, wherein each ring within A^1 and R^5 that contains from 3 to 8 ring atoms [and] may be substituted with 1 to 3 groups independently selected from (C_{1-6})alkyl, cyano, halo, nitro, halo-substituted (C_{1-6})alkyl, $-X^2OR^4$, $-X^2C(O)R^6$, $-X^2OC(O)R^6$, $-X^2C(O)OR^4$, $-X^2SR^4$, $-X^2S(O)R^6$, $-X^2S(O)_2R^6$, $-X^2NR^4R^4$, $-X^2NR^4C(O)R^6$, $-X^2NR^4C(O)OR^4$, $-X^2C(O)NR^4R^4$, $-X^2NR^4C(O)NR^4R^4$, $-X^2NR^4C(NR^4)NR^4R^4$, $-X^2NR^4S(O)_2R^6$ and $-X^2S(O)_2NR^4R^4$, wherein X^2 and R^4 are as defined above and R^6 is (C_{1-6})alkyl or halo-substituted (C_{1-6})alkyl, and wherein any said carbocycloalkyl and heterocycloalkyl rings within A^1 and R^5 may be substituted further with 1 to 2 groups independently selected from (C_{1-6})alkylidene, oxo, imino and thioxo, with the proviso that only one of A^1 and R^5 is a fused polycyclic ring system;

A^2 is a monocyclic [or fused bicyclic] ring selected from heteroarylene or unsaturated, partially unsaturated or saturated heterocycloalkylene containing a total of 5 to 11 ring atoms, wherein A^2 may be substituted with a group selected from $-X^2R^8$, $-X^2OR^8$, $-X^2C(O)R^8$, $-X^2OC(O)R^8$, $-X^2C(O)OR^8$, $-X^2SR^8$, $-X^2S(O)R^8$, $-X^2S(O)_2R^8$, $-X^2NR^4R^8$, $-X^2NR^4C(O)R^8$, $-X^2NR^4C(O)OR^8$, $-X^2C(O)NR^4R^8$, $-X^2NR^4C(O)NR^4R^8$, $-X^2NR^4C(NR^4)NR^4R^8$, $-X^2NR^4S(O)_2R^8$ and $-X^2S(O)_2NR^4R^8$, wherein X^2 is a bond or (C_{1-6})alkylene, R^8 is $-X^2R^9$ wherein X^2 is as defined above and R^9 is aryl containing a total of 6 to 10 ring atoms, heteroaryl containing a total of 5 to 10 ring atoms or unsaturated, partially unsaturated or saturated carbocycloalkyl or heterocycloalkyl each containing a total of 3 to 10 ring atoms, and R^4 at each occurrence independently is hydrogen, (C_{1-6})alkyl or halo-substituted (C_{1-6})alkyl, wherein each ring within A^2 and R^8 that contains from 3 to 8 ring atoms [and] may be substituted with 1 to 3 groups independently selected from (C_{1-6})alkyl, cyano, halo, nitro, halo-substituted (C_{1-6})alkyl, $-X^2OR^4$, $-X^2C(O)R^6$, $-X^2OC(O)R^6$, $-X^2C(O)OR^4$, $-X^2SR^4$, $-X^2S(O)R^6$, $-X^2S(O)_2R^6$, $-X^2NR^4R^4$, $-X^2NR^4C(O)R^6$, $-X^2NR^4C(O)OR^4$, $-X^2C(O)NR^4R^4$, $-X^2NR^4C(O)NR^4R^4$, $-X^2NR^4C(NR^4)NR^4R^4$, $-X^2C(O)NR^4X^2C(O)OR^4$, $-X^2NR^4S(O)_2R^6$ and $-X^2S(O)_2NR^4R^4$, wherein X^2 and R^4 are as defined above and R^6 is

(C_{1-6})alkyl or halo-substituted (C_{1-6})alkyl, and wherein any said heterocycloalkylene, carbocycloalkyl and heterocycloalkyl rings within A^2 and R^8 may be substituted further with 1 to 2 groups independently selected from (C_{1-6})alkylidene, oxo, imino and thioxo, with the proviso that only one of A^2 and R^8 is a fused polycyclic ring system; and

A^3 is a monocyclic or fused polycyclic ring system selected from aryl containing a total of 6 to 14 ring atoms, heteroaryl containing a total of 5 to 14 ring atoms and unsaturated, partially unsaturated or saturated carbocycloalkyl or heterocycloalkyl each containing a total of 3 to 14 ring atoms, wherein A^3 may be substituted with a group selected from $-X^2R^{9'}$, $-X^2OR^{9'}$, $-X^2C(O)R^{9'}$, $-X^2OC(O)R^{9'}$, $-X^2C(O)OR^{9'}$, $-X^2SR^{9'}$, $-X^2S(O)R^{9'}$, $-X^2S(O)_2R^{9'}$, $-X^2NR^4R^{9'}$, $-X^2NR^4C(O)R^{9'}$, $-X^2NR^4C(O)OR^{9'}$, $-X^2C(O)NR^4R^{9'}$, $-X^2NR^4C(O)NR^4R^{9'}$, $-X^2NR^4C(NR^4)NR^4R^{9'}$, $-X^2NR^4S(O)_2R^{9'}$ and $-X^2S(O)_2NR^4R^{9'}$ [$-X^2R^9$, $-X^2OR^9$, $-X^2C(O)R^9$, $-X^2OC(O)R^9$, $-X^2C(O)OR^9$, $-X^2SR^9$, $-X^2S(O)R^9$, $-X^2S(O)_2R^9$, $-X^2NR^4R^9$, $-X^2NR^4C(O)R^9$, $-X^2NR^4C(O)OR^9$, $-X^2C(O)NR^4R^9$, $-X^2NR^4C(O)NR^4R^9$, $-X^2NR^4C(NR^4)NR^4R^9$, $-X^2NR^4S(O)_2R^9$ and $-X^2S(O)_2NR^4R^9$,] wherein X^2 is a bond or (C_{1-6})alkylene, $R^{9'}$ [R^9] is $-X^2R^{10}$ wherein X^2 is as defined above and R^{10} is aryl containing a total of 6 to 10 ring atoms, heteroaryl containing a total of 5 to 10 ring atoms or unsaturated, partially unsaturated or saturated carbocycloalkyl or heterocycloalkyl each containing a total of 3 to 10 ring atoms, and R^4 at each occurrence independently is hydrogen, (C_{1-6})alkyl or halo-substituted (C_{1-6})alkyl, wherein each ring within A^3 and R^{10} that contains from 3 to 8 ring atoms [and] may be substituted with 1 to 3 groups independently selected from (C_{1-6})alkyl, cyano, halo, nitro, halo-substituted (C_{1-6})alkyl, $-X^2OR^4$, $-X^2C(O)R^6$, $-X^2OC(O)R^6$, $-X^2C(O)OR^4$, $-X^2SR^4$, $-X^2S(O)R^6$, $-X^2S(O)_2R^6$, $-X^2NR^4R^4$, $-X^2NR^4C(O)R^6$, $-X^2NR^4C(O)OR^4$, $-X^2C(O)NR^4R^4$, $-X^2NR^4C(O)NR^4R^4$, $-X^2NR^4C(NR^4)NR^4R^4$, $-X^2NR^4S(O)_2R^6$ and $-X^2S(O)_2NR^4R^4$, wherein X^2 and R^4 are as defined above and R^6 is (C_{1-6})alkyl or halo-substituted (C_{1-6})alkyl, and wherein any said carbocycloalkyl and heterocycloalkyl rings within A^3 and R^{10} may be substituted further with 1 to 2 groups independently selected from (C_{1-6})alkylidene, oxo, imino and thioxo, with the proviso that only one of A^3 and R^{10} is a fused polycyclic ring system; and the *N*-oxide derivatives, prodrug derivatives, protected derivatives, individual stereoisomers and mixtures of stereoisomers; and the pharmaceutically acceptable salts thereof;

with the proviso that when said compound is Formula II(a) [selected from the group consisting of Formulae II(a), II(b) and II(c)]:



II(a) II(b) II(c)

then A^3 is other than:

unsubstituted pyridyl;

unsubstituted thienyl;

unsubstituted indolyl;

unsubstituted phenyl;

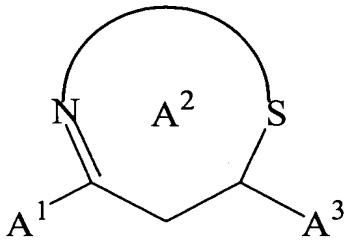
benzo[1,3]dioxolyl;

2,3-dihydro-benzo[1,4]dioxinyl;

phenyl which is mono-substituted by fluoro, bromo, iodo, nitro, methyl, isopropyl, ethoxy or methylsulfanyl; and

phenyl which is substituted by at least one of chloro, hydroxy or methoxy.

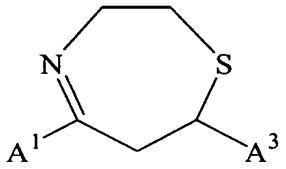
5. The compound of Claim 4 in which said compound is of Formula I(B):



I(B)

[in which R^1, A^1, A^2 and A^3 are defined as in Claim 1;] and the *N*-oxide derivatives, prodrug derivatives, protected derivatives, individual stereoisomers and mixtures of stereoisomers; and the pharmaceutically acceptable salts thereof.

6. The compound of Claim 5 in which said A^2 is 2,3,6,7-tetrahydro-[1,4]thiazepin-5,7-ylene, that is the compound of Formula I(C):



I(C)

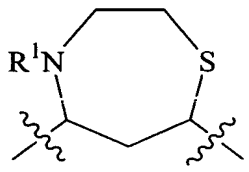
in which [A^1 and A^3 are defined as in Claim 1, and] said 2,3,6,7-tetrahydro-[1,4]thiazepin-5,7-ylene may be substituted with 1 to 3 groups independently selected from (C_{1-6})alkyl, cyano, halo, nitro, halo-substituted (C_{1-6})alkyl, $-X^2OR^4$, $-X^2C(O)R^6$, $-X^2OC(O)R^6$, $-X^2C(O)OR^4$, $-X^2SR^4$, $-X^2S(O)R^6$, $-X^2S(O)_2R^6$, $-X^2NR^4R^4$, $-X^2NR^4C(O)R^6$, $-X^2NR^4C(O)OR^4$, $-X^2C(O)NR^4R^4$, $-X^2NR^4C(O)NR^4R^4$, $-X^2NR^4C(NR^4)NR^4R^4$, $-X^2C(O)NR^4X^2C(O)OR^4$, $-X^2NR^4S(O)_2R^6$ and $-X^2S(O)_2NR^4R^4$, wherein X^2 is a bond or (C_{1-6})alkylene, R^4 at each occurrence independently is hydrogen, (C_{1-6})alkyl or halo-substituted (C_{1-6})alkyl, and R^6 is (C_{1-6})alkyl or halo-substituted (C_{1-6})alkyl; and the *N*-oxide derivatives, prodrug derivatives, protected derivatives, individual stereoisomers and mixtures of stereoisomers; and the pharmaceutically acceptable salts thereof.

14. The compound of Claim 13 which is:

3-[7-(2,4-dimethoxy-phenyl)-2,3,6,[,]7-tetrahydro-[1,4]thiazepin-5-yl]-4-hydroxy-1*H*-quinolin-2-one;

and the *N*-oxide derivatives, prodrug derivatives, protected derivatives; and the pharmaceutically acceptable salts thereof.

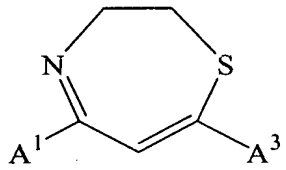
22. The compound of Claim 4 in which said A^2 is a group of Formula (k):



(k)

in which [R^1 is defined as in Claim 1 and] said group of Formula (k) may be substituted with 1 to 3 groups independently selected from (C_{1-6})alkyl, cyano, halo, nitro, halo-substituted (C_{1-6})alkyl, $-X^2OR^4$, $-X^2C(O)R^6$, $-X^2OC(O)R^6$, $-X^2C(O)OR^4$, $-X^2SR^4$, $-X^2S(O)R^6$, $-X^2S(O)_2R^6$, $-X^2NR^4R^4$, $-X^2NR^4C(O)R^6$, $-X^2NR^4C(O)OR^4$, $-X^2C(O)NR^4R^4$, $-X^2NR^4C(O)NR^4R^4$, $-X^2NR^4C(NR^4)NR^4R^4$, $-X^2C(O)NR^4X^2C(O)OR^4$, $-X^2NR^4S(O)_2R^6$ and $-X^2S(O)_2NR^4R^4$, wherein X^2 is a bond or (C_{1-6})alkylene, R^4 at each occurrence independently is hydrogen, (C_{1-6})alkyl or halo-substituted (C_{1-6})alkyl, and R^6 is (C_{1-6})alkyl or halo-substituted (C_{1-6})alkyl; and the *N*-oxide derivatives, prodrug derivatives, protected derivatives, individual stereoisomers and mixtures of stereoisomers; and the pharmaceutically acceptable salts thereof.

28. The compound of Claim 4 in which said A^2 is 2,3-dihydro-[1,4]thiazepin-5,7-ylene that is the compound of Formula I(F):

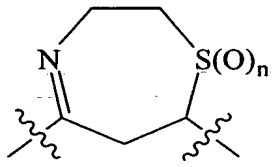


I(F)

in which [A^1 and A^3 are defined as in Claim 1, and] said 2,3-dihydro-[1,4]thiazepin-5,7-ylene may be substituted with 1 to 3 groups independently selected from (C_{1-6})alkyl, cyano, halo, nitro, halo-substituted (C_{1-6})alkyl, $-X^2OR^4$, $-X^2C(O)R^6$, $-X^2OC(O)R^6$, $-X^2C(O)OR^4$, $-X^2SR^4$, $-X^2S(O)R^6$, $-X^2S(O)_2R^6$, $-X^2NR^4R^4$, $-X^2NR^4C(O)R^6$, $-X^2NR^4C(O)OR^4$, $-X^2C(O)NR^4R^4$, $-X^2NR^4C(O)NR^4R^4$, $-X^2NR^4C(NR^4)NR^4R^4$, $-X^2C(O)NR^4X^2C(O)OR^4$, $-X^2NR^4S(O)_2R^6$ and $-X^2S(O)_2NR^4R^4$, wherein X^2 is a bond or (C_{1-6})alkylene, R^4 at each occurrence independently is hydrogen, (C_{1-6})alkyl or halo-substituted (C_{1-6})alkyl, and R^6 is (C_{1-6})alkyl or halo-substituted (C_{1-6})alkyl; and the *N*-oxide derivatives, prodrug derivatives,

protected derivatives, individual stereoisomers and mixtures of stereoisomers; and the pharmaceutically acceptable salts thereof.

36. The compound of Claim 35 in which A^2 is a group of Formula (l):



(l)

in which [n, and R^1 are defined as in Claim 1 and] said group of Formula (l) may be substituted with 1 to 3 groups independently selected from (C_{1-6})alkyl, cyano, halo, nitro, halo-substituted (C_{1-6})alkyl, $-X^2OR^4$, $-X^2C(O)R^6$, $-X^2OC(O)R^6$, $-X^2C(O)OR^4$, $-X^2SR^4$, $-X^2S(O)R^6$, $-X^2S(O)_2R^6$, $-X^2NR^4R^4$, $-X^2NR^4C(O)R^6$, $-X^2NR^4C(O)OR^4$, $-X^2C(O)NR^4R^4$, $-X^2NR^4C(O)NR^4R^4$, $-X^2NR^4C(NR^4)NR^4R^4$, $-X^2C(O)NR^4X^2C(O)OR^4$, $-X^2NR^4S(O)_2R^6$ and $-X^2S(O)_2NR^4R^4$, wherein X^2 is a bond or (C_{1-6})alkylene, R^4 at each occurrence independently is hydrogen, (C_{1-6})alkyl or halo-substituted (C_{1-6})alkyl, and R^6 is (C_{1-6})alkyl or halo-substituted (C_{1-6})alkyl; and the *N*-oxide derivatives, prodrug derivatives, protected derivatives, individual stereoisomers and mixtures of stereoisomers; and the pharmaceutically acceptable salts thereof.

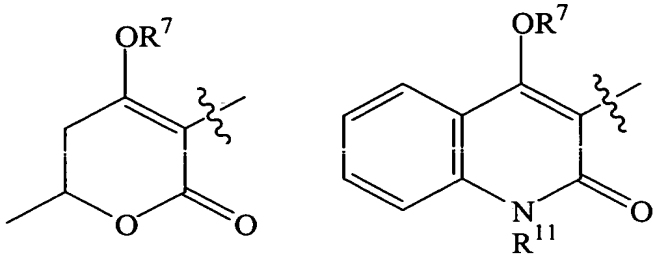
48. A compound selected from the group consisting of:

7-(2,4-dimethoxy-phenyl)-5-(4-hydroxy-6-methyl-2-oxo-2*H*-pyran-3-yl)-2,2-dimethyl-2,3,6,7-tetrahydro-[1,4]thiazepine-3-carboxylic acid; and

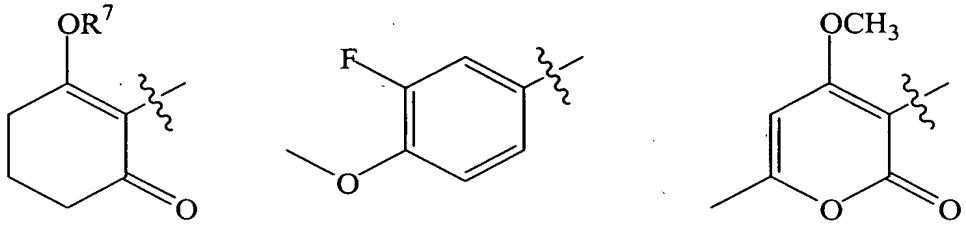
2-({1-[7-(2,4-dimethoxy-phenyl)-5-(4-hydroxy-6-methyl-2-oxo-2*H*-pyran-3-yl)-2,2-dimethyl-2,3,6,7-tetrahydro-[1,4]thiazepin-3-yl]-methanoyl}-amino)-propionic acid *tert*-butyl ester;

and the *N*-oxide derivatives, prodrug derivatives, protected derivatives; and the pharmaceutically acceptable salts thereof.[.]

49. The compound of Claim 1 in which A^1 is a group selected from Formulae (b), (c), (d), (e) and (f):



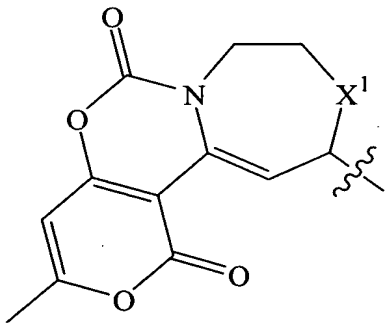
(b) (c)



(d) (e) (f)

in which R^7 is hydrogen or methyl, R^{11} is hydrogen or (C_{1-6})alkyl and the free valance is attached to A^2[, or

A^2 and A^1 together with R^1 and the atoms to which A^1 and R^1 are attached forms a group of Formula (g):



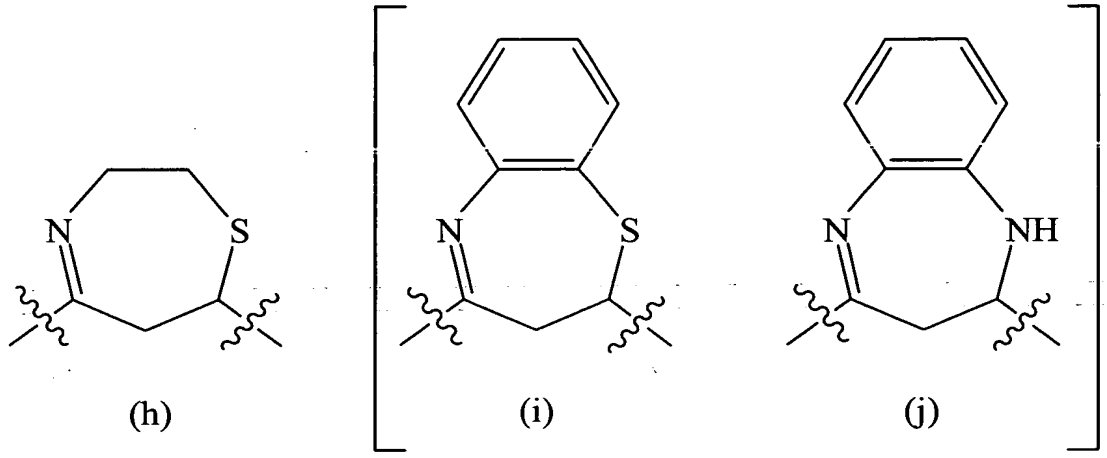
(g)

wherein X^1 is -S- and the free valance is attached to A^3]; and

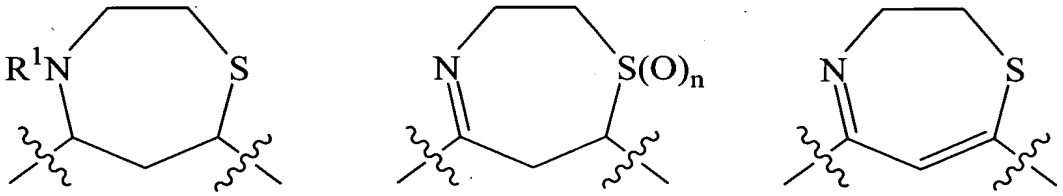
A^2 is as defined above or is a monocyclic [or fused bicyclic] ring selected from heteroarylene or unsaturated, partially unsaturated or saturated heterocycloalkylene containing a total of 5 to 11 ring atoms, wherein A^2 may be substituted with a group selected from $-X^2R^8$, $-X^2OR^8$, $-X^2C(O)R^8$, $-X^2OC(O)R^8$, $-X^2C(O)OR^8$, $-X^2SR^8$, $-X^2S(O)R^8$, $-X^2S(O)_2R^8$, $-X^2NR^4R^8$, $-X^2NR^4C(O)R^8$, $-X^2NR^4C(O)OR^8$, $-X^2C(O)NR^4R^8$,

$-X^2NR^4C(O)NR^4R^8$, $-X^2NR^4C(NR^4)NR^4R^8$, $-X^2NR^4S(O)_2R^8$ and $-X^2S(O)_2NR^4R^8$, wherein X^2 is a bond or (C_{1-6})alkylene, R^8 is $-X^2R^9$ wherein X^2 is as defined above and R^9 is aryl containing a total of 6 to 10 ring atoms, heteroaryl containing a total of 5 to 10 ring atoms or unsaturated, partially unsaturated or saturated carbocycloalkyl or heterocycloalkyl each containing a total of 3 to 10 ring atoms, and R^4 at each occurrence independently is hydrogen, (C_{1-6})alkyl or halo-substituted (C_{1-6})alkyl, wherein each ring within A^2 and R^8 that contains from 3 to 8 ring atoms [and] may be substituted with 1 to 3 groups independently selected from (C_{1-6})alkyl, cyano, halo, nitro, halo-substituted (C_{1-6})alkyl, $-X^2OR^4$, $-X^2C(O)R^6$, $-X^2OC(O)R^6$, $-X^2C(O)OR^4$, $-X^2SR^4$, $-X^2S(O)R^6$, $-X^2S(O)_2R^6$, $-X^2NR^4R^4$, $-X^2NR^4C(O)R^6$, $-X^2NR^4C(O)OR^4$, $-X^2C(O)NR^4R^4$, $-X^2NR^4C(O)NR^4R^4$, $-X^2NR^4C(NR^4)NR^4R^4$, $-X^2C(O)NR^4X^2C(O)OR^4$, $-X^2NR^4S(O)_2R^6$ and $-X^2S(O)_2NR^4R^4$, wherein X^2 and R^4 are as defined above and R^6 is (C_{1-6})alkyl or halo-substituted (C_{1-6})alkyl, and wherein any said heterocycloalkylene [heteroalkylene], carbocycloalkyl and heterocycloalkyl rings within A^2 and R^8 may be substituted further with 1 to 2 groups independently selected from (C_{1-6})alkylidene, oxo, imino and thioxo, with the proviso that only one of A^2 and R^8 is a fused polycyclic ring system; and the *N*-oxide derivatives, prodrug derivatives, protected derivatives, individual stereoisomers and mixtures of stereoisomers; and the pharmaceutically acceptable salts thereof.

50. The compound of Claim 49 in which A^2 is a group selected from Formulae (h), [(i), (j),] (k), (l) and (m):

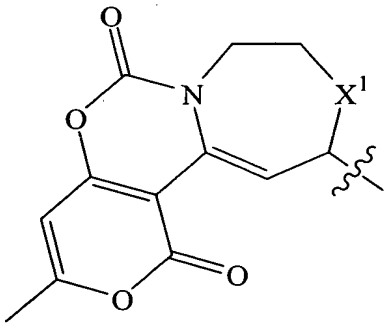


(h) (i) (j)



(k) (l) (m)

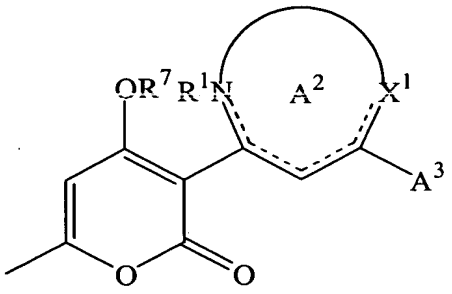
in which n is 1 or 2 and R^1 is acetyl or trifluoroacetyl [or A^2 and A^1 together with R^1 and the atoms to which A^1 and R^1 are attached forms a group of Formula (g):



(g)

wherein X^1 is -S- and the free valance is attached to A^3]; and the *N*-oxide derivatives, prodrug derivatives, protected derivatives, individual stereoisomers and mixtures of stereoisomers; and the pharmaceutically acceptable salts thereof.

51. A compound of Formula II:



II

in which:

the dashed lines indicate optional unsaturation without violating valency rules;

R^1 is hydrogen, (C_{1-6})alkyl or $-C(O)R^6$, wherein R^6 is as defined below, or R^1 is absent when a double bond exists between the nitrogen atom to which R^1 is attached and an adjacent ring atom or R^1 is as defined below;

R^7 is hydrogen;

X^1 is $-S(O)_n-$, wherein n is 0, 1, or 2 [$-NR^2-$, -S-, -S(O)-, $-S(O)_2-$ or -O-, wherein R^2 is hydrogen or (C_{1-6})alkyl or is absent when a double bond exists between the nitrogen atom to which R^2 is attached and an adjacent ring atom];

A^2 is a monocyclic [or fused bicyclic] ring selected from heteroarylene or unsaturated, partially unsaturated or saturated heterocycloalkylene containing a total of 5 to 11 ring atoms, wherein A^2 may be substituted with a group selected from $-R^8$, $-X^2OR^8$, $-X^2C(O)R^8$, $-X^2OC(O)R^8$, $-X^2C(O)OR^8$, $-X^2SR^8$, $-X^2S(O)R^8$, $-X^2S(O)_2R^8$, $-X^2NR^4R^8$, $-X^2NR^4C(O)R^8$, $-X^2NR^4C(O)OR^8$, $-X^2C(O)NR^4R^8$, $-X^2NR^4C(O)NR^4R^8$, $-X^2NR^4C(NR^4)NR^4R^8$, $-X^2NR^4S(O)_2R^8$ and $-X^2S(O)_2NR^4R^8$, wherein X^2 is a bond or (C_{1-6})alkylene, R^8 is $-X^2R^9$ wherein X^2 is as defined above and R^9 is aryl containing a total of 6 to 10 ring atoms, heteroaryl containing a total of 5 to 10 ring atoms or unsaturated, partially unsaturated or saturated carbocycloalkyl or heterocycloalkyl each containing a total of 3 to 10 ring atoms, and R^4 at each occurrence independently is hydrogen, (C_{1-6})alkyl or halo-substituted (C_{1-6})alkyl, wherein each ring within A^2 and R^8 that contains from 3 to 8 ring atoms [and] may be substituted with 1 to 3 groups independently selected from (C_{1-6})alkyl, cyano, halo, nitro, halo-substituted (C_{1-6})alkyl, $-X^2OR^4$, $-X^2C(O)R^6$, $-X^2OC(O)R^6$, $-X^2C(O)OR^4$, $-X^2SR^4$, $-X^2S(O)R^6$, $-X^2S(O)_2R^6$, $-X^2NR^4R^4$, $-X^2NR^4C(O)R^6$, $-X^2C(O)NR^4R^4$,

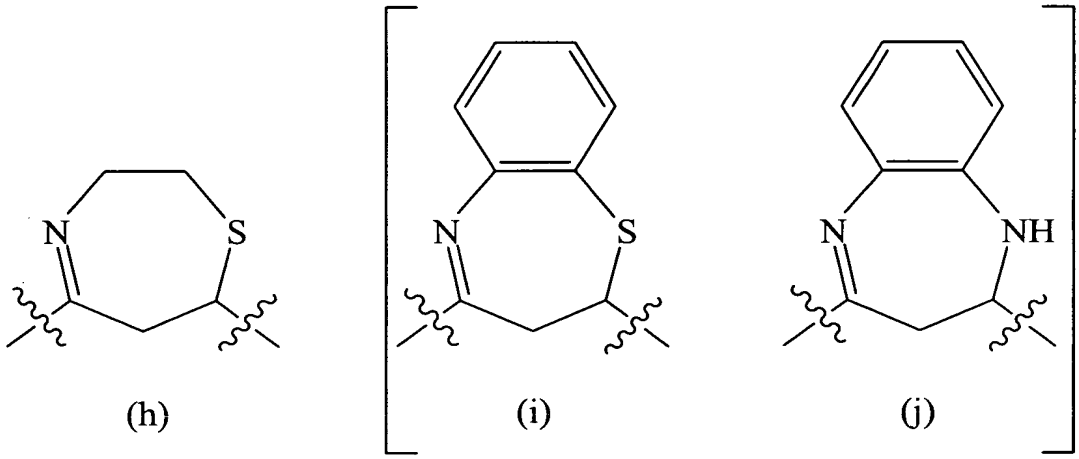
$-X^2NR^4C(O)NR^4R^4$, $-X^2NR^4C(NR^4)NR^4R^4$, $-X^2C(O)NR^4X^2C(O)OR^4$, $-X^2NR^4S(O)_2R^6$ and $-X^2S(O)_2NR^4R^4$, wherein X^2 and R^4 are as defined above and R^6 is (C_{1-6})alkyl or halo-substituted (C_{1-6})alkyl, and wherein any said heterocycloalkylene [heteroalkylene], carbocycloalkyl and heterocycloalkyl rings within A^2 and R^8 may be substituted further with 1 to 2 groups independently selected from (C_{1-6})alkylidene, oxo, imino and thioxo with the proviso that only one of A^2 and R^8 is a fused polycyclic ring system; and

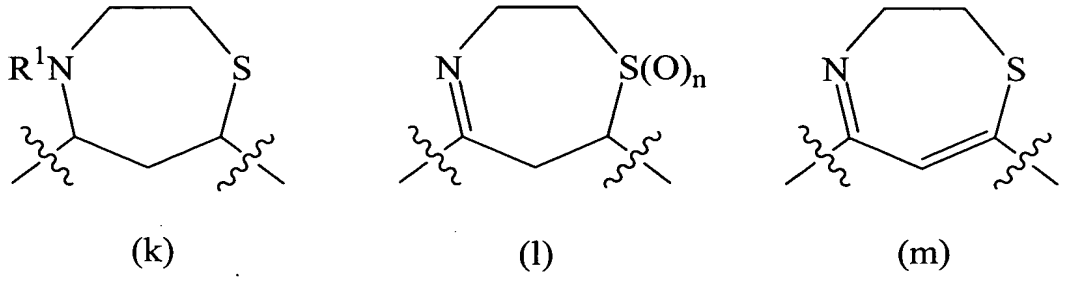
A^3 is a monocyclic or fused polycyclic ring system selected from aryl containing a total of 6 to 14 ring atoms, heteroaryl containing a total of 5 to 14 ring atoms and unsaturated, partially unsaturated or saturated carbocycloalkyl or heterocycloalkyl each containing a total of 3 to 14 ring atoms, wherein A^3 may be substituted with a group selected from $-R^{9'}$, $-X^2OR^{9'}$, $-X^2C(O)R^{9'}$, $-X^2OC(O)R^{9'}$, $-X^2C(O)OR^{9'}$, $-X^2SR^{9'}$, $-X^2S(O)R^{9'}$, $-X^2S(O)_2R^{9'}$, $-X^2NR^4R^{9'}$, $-X^2NR^4C(O)R^{9'}$, $-X^2NR^4C(O)OR^{9'}$, $-X^2C(O)NR^4R^{9'}$, $-X^2NR^4C(O)NR^4R^{9'}$, $-X^2NR^4C(NR^4)NR^4R^{9'}$, $-X^2NR^4S(O)_2R^{9'}$ and $-X^2S(O)_2NR^4R^{9'}$ [$-R^9$, $-X^2OR^9$, $-X^2C(O)R^9$, $-X^2OC(O)R^9$, $-X^2C(O)OR^9$, $-X^2SR^9$, $-X^2S(O)R^9$, $-X^2S(O)_2R^9$, $-X^2NR^4R^9$, $-X^2NR^4C(O)R^9$, $-X^2NR^4C(O)OR^9$, $-X^2C(O)NR^4R^9$, $-X^2NR^4C(O)NR^4R^9$, $-X^2NR^4C(NR^4)NR^4R^9$, $-X^2NR^4S(O)_2R^9$ and $-X^2S(O)_2NR^4R^9$], wherein X^2 is a bond or (C_{1-6})alkylene, $R^{9'}$ [R^9] is $-X^2R^{10}$ wherein X^2 is as defined above and R^{10} is aryl containing a total of 6 to 10 ring atoms, heteroaryl containing a total of 5 to 10 ring atoms or unsaturated, partially unsaturated or saturated carbocycloalkyl or heterocycloalkyl each containing a total of 3 to 10 ring atoms, and R^4 at each occurrence independently is hydrogen, (C_{1-6})alkyl or halo-substituted (C_{1-6})alkyl, wherein each ring within A^3 and R^{10} that contains from 3 to 8 ring atoms [and] may be substituted with 1 to 3 groups independently selected from (C_{1-6})alkyl, cyano, halo, nitro, halo-substituted (C_{1-6})alkyl, $-X^2OR^4$, $-X^2C(O)R^6$, $-X^2OC(O)R^6$, $-X^2C(O)OR^4$, $-X^2SR^4$, $-X^2S(O)R^6$, $-X^2S(O)_2R^6$, $-X^2NR^4R^4$, $-X^2NR^4C(O)R^6$, $-X^2NR^4C(O)OR^4$, $-X^2C(O)NR^4R^4$, $-X^2NR^4C(O)NR^4R^4$, $-X^2NR^4C(NR^4)NR^4R^4$, $-X^2NR^4S(O)_2R^6$ and $-X^2S(O)_2NR^4R^4$, wherein X^2 and R^4 are as defined above and R^6 is (C_{1-6})alkyl or halo-substituted (C_{1-6})alkyl, and wherein any said carbocycloalkyl and heterocycloalkyl rings within A^3 and R^{10} may be substituted further with 1 to 2 groups independently selected from (C_{1-6})alkylidene, oxo, imino and thioxo with the proviso that only one of A^3 and R^{10} is a fused polycyclic ring system; and the *N*-oxide derivatives,

prodrug derivatives, protected derivatives, individual stereoisomers and mixtures of stereoisomers; and the pharmaceutically acceptable salts thereof;

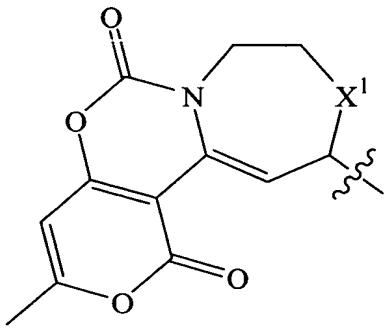
provided, however, Formula II does not represent a compound wherein A^2 is 2,3,6,7-tetrahydro-[1,4]thiazepinylene [, 2,3-dihydro-benzo[*b*][1,4]thiazepinylene or 7-trifluoro-2,3-dihydro-benzo[*b*][1,4]thiazepinylene] and A^3 is benzo[1,3]dioxolyl, indolyl, phenyl, pyridyl or thienyl, wherein said phenyl may be substituted with 1 to 3 groups independently selected from halo, nitro, hydroxy, (C_{1-4})alkyl, (C_{1-4})alkylsulfanyl and (C_{1-4})alkyloxy or any *N*-oxide derivative; protected derivative, individual stereoisomer or mixture of stereoisomers, or pharmaceutically acceptable salt thereof.

52. The compound of Claim 51 in which A^2 is a group selected from Formulae (h), [(i), (j),] (k), (l) and (m):





in which n is 1 or 2 and R^1 is acetyl or trifluoroacetyl [or A^2 and A^1 together with R^1 and the atoms to which A^1 and R^1 are attached forms a group of Formula (g):



(g)

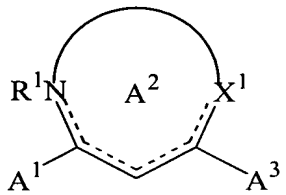
wherein X^1 is -S- and the free valance is attached to A^3]; and the *N*-oxide derivatives, prodrug derivatives, protected derivatives, individual stereoisomers and mixtures of stereoisomers; and the pharmaceutically acceptable salts thereof.

53. The compound of Claim 52 in which A^3 is phenyl or heteroaryl containing a total of 5 to 9 ring atoms, wherein A^3 may be substituted with a group selected from $-R^{9'}$, $-X^2OR^{9'}$, $-X^2SR^{9'}$ and $-X^2S(O)_2R^{9'}$ [$-R^9$, $-X^2OR^9$, $-X^2SR^9$ and $-X^2S(O)_2R^9$], wherein $R^{9'}$ [R^9] is $-X^2R^{10}$, X^2 is a bond or (C_{1-6})alkylene and R^{10} is phenyl or heteroaryl containing a total of 5 to 6 ring atoms, wherein each ring within A^3 and R^{10} may be substituted with 1 to 3 groups independently selected from (C_{1-6})alkyl, halo, halo-substituted (C_{1-6})alkyl, $-X^2OR^4$, $-X^2SR^4$, $-X^2S(O)_2R^6$ and $-X^2NR^4R^4$, wherein R^4 at each occurrence independently is hydrogen, (C_{1-6})alkyl or halo-substituted (C_{1-6})alkyl and R^6 is (C_{1-6})alkyl or halo-substituted (C_{1-6})alkyl; and the *N*-oxide derivatives, prodrug derivatives, protected derivatives, individual stereoisomers and mixtures of stereoisomers; and the pharmaceutically acceptable salts thereof.

56. (once amended) The pharmaceutical composition of Claim 55, wherein said cancer therapeutic agent is selected from the group consisting of busulfan, cis-platin, mitomycin C, carboplatin, colchicine, vinblastine, paclitaxel, docetaxel, camptothecin, topotecan, doxorubicin, etoposide, 5-azacytidine, 5-fluorouracil, methotrexate, 5-fluoro-2'-deoxy-uridine, ara-C, hydroxyurea, thioguanine, melphalan, chlorambucil,

cyclophosamide, ifosfamide, vincristine, mitoguazone, epirubicin, aclarubicin, bleomycin, imitoxantrone, elliptinium, fludarabine, octreotide, retinoic acid, tamoxifen, HERCEPTIN (trastuzumab), RITUXAN (rituximab) [Herceptin®, Rituxan®] and alanosine.

57. A method of treating a disorder responsive to the induction of apoptosis in an animal suffering said disorder, comprising administering to a mammal in need of such treatment an effective amount of a compound of Formula I:



I

in which:

the dashed lines indicate optional unsaturation without violating valency rules;

R^1 is hydrogen, (C_{1-6})alkyl or $-C(O)R^6$, wherein R^6 is as defined below, or R^1 is absent when a double bond exists between the nitrogen atom to which R^1 is attached and an adjacent ring atom or R^1 is as defined below;

X^1 is $-S(O)_n-$, wherein n is 0, 1, or 2 [$-NR^2-$, -S-, -S(O)-, $-S(O)_2-$ or -O-, wherein R^2 is hydrogen or (C_{1-6})alkyl or is absent when a double bond exists between the nitrogen atom to which R^2 is attached and an adjacent ring atom];

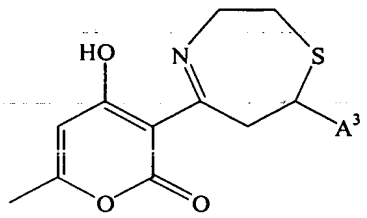
A^1 is a monocyclic or fused polycyclic ring system selected from aryl containing a total of 6 to 14 ring atoms, heteroaryl containing a total of 5 to 14 ring atoms and unsaturated, partially unsaturated or saturated carbocycloalkyl or heterocycloalkyl each containing a total of 3 to 14 ring atoms, [or A^1 together with R^1 and the atoms to which A^1 and R^1 are attached forms a fused polycyclic ring system selected from heteroaryl and unsaturated, partially unsaturated or saturated heterocycloalkyl in any case containing a total of 10 to 15 ring atoms,] wherein A^1 may be substituted with a group selected from $-R^3$, $-X^2OR^3$, $-X^2C(O)R^3$, $-X^2OC(O)R^3$, $-X^2C(O)OR^3$, $-X^2SR^3$, $-X^2S(O)R^3$, $-X^2S(O)_2R^3$, $-X^2NR^3R^4$, $-X^2NR^4C(O)R^3$, $-X^2NR^4C(O)OR^3$, $-X^2C(O)NR^3R^4$, $-X^2NR^4C(O)NR^3R^4$, $-X^2NR^4C(NR^4)NR^3R^4$, $-X^2NR^4S(O)_2R^3$ and $-X^2S(O)_2NR^3R^4$, wherein X^2 is a bond or (C_{1-6})alkylene, R^3 is $-X^2R^5$ wherein X^2 is as defined above and R^5 is aryl containing a total

of 6 to 10 ring atoms, heteroaryl containing a total of 5 to 10 ring atoms or unsaturated, partially unsaturated or saturated carbocycloalkyl or heterocycloalkyl each containing a total of 3 to 10 ring atoms, and R^4 at each occurrence independently is hydrogen, (C_{1-6})alkyl or halo-substituted (C_{1-6})alkyl, wherein each ring within A^1 and R^5 that contains from 3 to 8 ring atoms [and] may be substituted with 1 to 3 groups independently selected from (C_{1-6})alkyl, cyano, halo, nitro, halo-substituted (C_{1-6})alkyl, $-X^2OR^4$, $-X^2C(O)R^6$, $-X^2OC(O)R^6$, $-X^2C(O)OR^4$, $-X^2SR^4$, $-X^2S(O)R^6$, $-X^2S(O)_2R^6$, $-X^2NR^4R^4$, $-X^2NR^4C(O)R^6$, $-X^2NR^4C(O)OR^4$, $-X^2C(O)NR^4R^4$, $-X^2NR^4C(O)NR^4R^4$, $-X^2NR^4C(NR^4)NR^4R^4$, $-X^2NR^4S(O)_2R^6$ and $-X^2S(O)_2NR^4R^4$, wherein X^2 and R^4 are as defined above and R^6 is (C_{1-6})alkyl or halo-substituted (C_{1-6})alkyl, and wherein any said carbocycloalkyl and heterocycloalkyl rings within A^1 and R^5 may be substituted further with 1 to 2 groups independently selected from (C_{1-6})alkylidene, oxo, imino and thioxo, with the provisos that only one of A^1 and R^5 is a fused polycyclic ring system;

A^2 is a monocyclic [or fused bicyclic] ring selected from heteroarylene or unsaturated, partially unsaturated or saturated heterocycloalkylene containing a total of 5 to 11 ring atoms, wherein A^2 may be substituted with a group selected from $-R^8$, $-X^2OR^8$, $-X^2C(O)R^8$, $-X^2OC(O)R^8$, $-X^2C(O)OR^8$, $-X^2SR^8$, $-X^2S(O)R^8$, $-X^2S(O)_2R^8$, $-X^2NR^4R^8$, $-X^2NR^4C(O)R^8$, $-X^2NR^4C(O)OR^8$, $-X^2C(O)NR^4R^8$, $-X^2NR^4C(O)NR^4R^8$, $-X^2NR^4C(NR^4)NR^4R^8$, $-X^2NR^4S(O)_2R^8$ and $-X^2S(O)_2NR^4R^8$, wherein X^2 is a bond or (C_{1-6})alkylene, R^8 is $-X^2R^9$ wherein X^2 is as defined above and R^9 is aryl containing a total of 6 to 10 ring atoms, heteroaryl containing a total of 5 to 10 ring atoms or unsaturated, partially unsaturated or saturated carbocycloalkyl or heterocycloalkyl each containing a total of 3 to 10 ring atoms, and R^4 at each occurrence independently is hydrogen, (C_{1-6})alkyl or halo-substituted (C_{1-6})alkyl, wherein each ring within A^2 and R^8 that contains from 3 to 8 ring atoms [and] may be substituted with 1 to 3 groups independently selected from (C_{1-6})alkyl, cyano, halo, nitro, halo-substituted (C_{1-6})alkyl, $-X^2OR^4$, $-X^2C(O)R^6$, $-X^2OC(O)R^6$, $-X^2C(O)OR^4$, $-X^2SR^4$, $-X^2S(O)R^6$, $-X^2S(O)_2R^6$, $-X^2NR^4R^4$, $-X^2NR^4C(O)R^6$, $-X^2NR^4C(O)OR^4$, $-X^2C(O)NR^4R^4$, $-X^2NR^4C(O)NR^4R^4$, $-X^2NR^4C(NR^4)NR^4R^4$, $-X^2C(O)NR^4X^2C(O)OR^4$, $-X^2NR^4S(O)_2R^6$ and $-X^2S(O)_2NR^4R^4$, wherein X^2 and R^4 are as defined above and R^6 is (C_{1-6})alkyl or halo-substituted (C_{1-6})alkyl, and wherein any said heterocycloalkylene, carbocycloalkyl and heterocycloalkyl rings within A^2 and R^8 may be substituted further with

1 to 2 groups independently selected from (C_{1-6})alkylidene, oxo, imino and thioxo, with the proviso that only one of A^2 and R^8 is a fused polycyclic ring system; and

A^3 is a monocyclic or fused polycyclic ring system selected from aryl containing a total of 6 to 14 ring atoms, heteroaryl containing a total of 5 to 14 ring atoms and unsaturated, partially unsaturated or saturated carbocycloalkyl or heterocycloalkyl each containing a total of 3 to 14 ring atoms, wherein A^3 may be substituted with a group selected from $\underline{-R^{9'}}$, $\underline{-X^2OR^{9'}}$, $\underline{-X^2C(O)R^{9'}}$, $\underline{-X^2OC(O)R^{9'}}$, $\underline{-X^2C(O)OR^{9'}}$, $\underline{-X^2SR^{9'}}$, $\underline{-X^2S(O)R^{9'}}$, $\underline{-X^2S(O)_2R^{9'}}$, $\underline{-X^2NR^4R^{9'}}$, $\underline{-X^2NR^4C(O)R^{9'}}$, $\underline{-X^2NR^4C(O)OR^{9'}}$, $\underline{-X^2C(O)NR^4R^{9'}}$, $\underline{-X^2NR^4C(O)NR^4R^{9'}}$, $\underline{-X^2NR^4C(NR^4)NR^4R^{9'}}$, $\underline{-X^2NR^4S(O)_2R^{9'}}$ and $\underline{-X^2S(O)_2NR^4R^{9'}}$ [$-R^9$, $-X^2OR^9$, $-X^2C(O)R^9$, $-X^2OC(O)R^9$, $-X^2C(O)OR^9$, $-X^2SR^9$, $-X^2S(O)R^9$, $-X^2S(O)_2R^9$, $-X^2NR^4R^9$, $-X^2NR^4C(O)R^9$, $-X^2NR^4C(O)OR^9$, $-X^2C(O)NR^4R^9$, $-X^2NR^4C(O)NR^4R^9$, $-X^2NR^4C(NR^4)NR^4R^9$, $-X^2NR^4S(O)_2R^9$ and $-X^2S(O)_2NR^4R^9$], wherein X^2 is a bond or (C_{1-6})alkylene, $\underline{R^{9'}}$ [R^9] is $-X^2R^{10}$ wherein X^2 is as defined above and R^{10} is aryl containing a total of 6 to 10 ring atoms, heteroaryl containing a total of 5 to 10 ring atoms or unsaturated, partially unsaturated or saturated carbocycloalkyl or heterocycloalkyl each containing a total of 3 to 10 ring atoms, and R^4 at each occurrence independently is hydrogen, (C_{1-6})alkyl or halo-substituted (C_{1-6})alkyl, wherein each ring within A^3 and R^{10} $\underline{\text{that}}$ contains from 3 to 8 ring atoms [and] may be substituted with 1 to 3 groups independently selected from (C_{1-6})alkyl, cyano, halo, nitro, halo-substituted (C_{1-6})alkyl, $-X^2OR^4$, $-X^2C(O)R^6$, $-X^2OC(O)R^6$, $-X^2C(O)OR^4$, $-X^2SR^4$, $-X^2S(O)R^6$, $-X^2S(O)_2R^6$, $-X^2NR^4R^4$, $-X^2NR^4C(O)R^6$, $-X^2NR^4C(O)OR^4$, $-X^2C(O)NR^4R^4$, $-X^2NR^4C(O)NR^4R^4$, $-X^2NR^4C(NR^4)NR^4R^4$, $-X^2NR^4S(O)_2R^6$ and $-X^2S(O)_2NR^4R^4$, wherein X^2 and R^4 are as defined above and R^6 is (C_{1-6})alkyl or halo-substituted (C_{1-6})alkyl, and wherein any said carbocycloalkyl and heterocycloalkyl rings within A^3 and R^{10} may be substituted further with 1 to 2 groups independently selected from (C_{1-6})alkylidene, oxo, imino and thioxo, with the proviso that only one of A^3 and R^{10} is a fused polycyclic ring system; or an *N*-oxide derivative, prodrug derivative, protected derivative, individual stereoisomer or mixture of stereoisomers, or a pharmaceutically acceptable salt thereof; with the proviso that when said compound is of Formula II(a):



II(a)

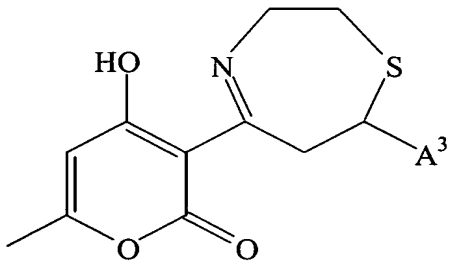
then A^3 is other than:

(a) benzo[1,3]dioxolyl;

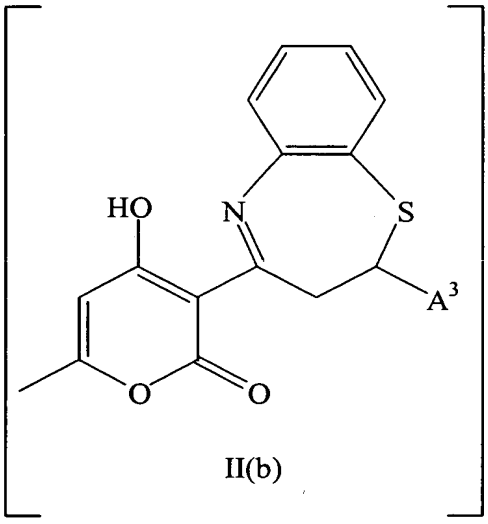
(b) phenyl which is mono-substituted by bromo, hydroxy, methyl or isopropyl; and

(c) phenyl which is substituted by at least one of Cl and methoxy and not substituted by methylsulfanyl, amino, methylamino and dimethylamino.

58. The method of claim 57, with the further proviso that when said compound is [selected from the group consisting of] Formula II(a) [and II(b)]:



II(a)



II(b)

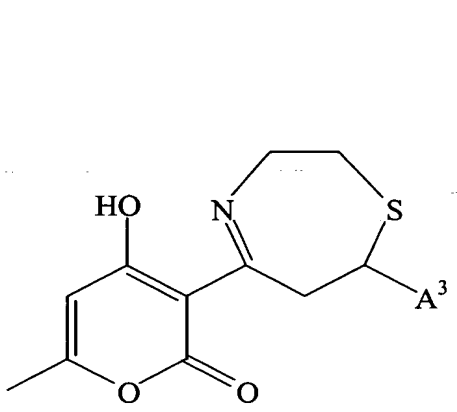
then A^3 is other than:

(a) benzo[1,3]dioxolyl;

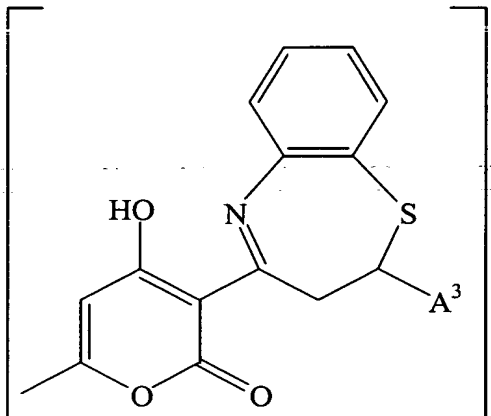
(b) phenyl which is mono-substituted by bromo, nitro, hydroxy, methyl, or isopropyl; and

(c) phenyl which is substituted by at least one of Cl and methoxy and not substituted by methylsulfanyl, amino, methylamino and dimethylamino.

59. The method of claim 57, with the further proviso that when said compound is [selected from the group consisting of] Formula II(a) [and II(b)]:



II(a)



II(b)

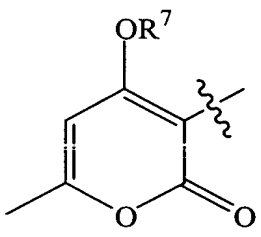
then A^3 is other than:

(a) benzo[1,3]dioxolyl;

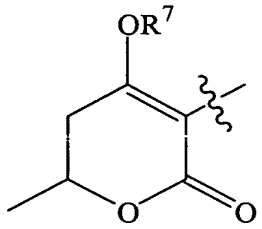
(b) 2,3-dihydro-benzo[1,4]dioxinyl; and

(c) phenyl which is substituted by at least one of bromo, chloro, hydroxy, nitro, methoxy and $(C_{1-\underline{6}[3]})$alkyl.

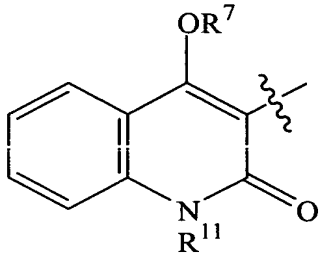
60. The method of Claim 57, wherein A^1 of said compound is a group selected from Formulae (a), (b), (c), (d) and (e):



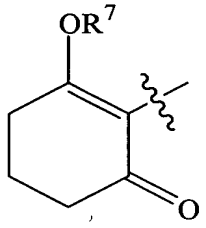
(a)



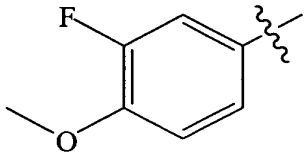
(b)



(c)



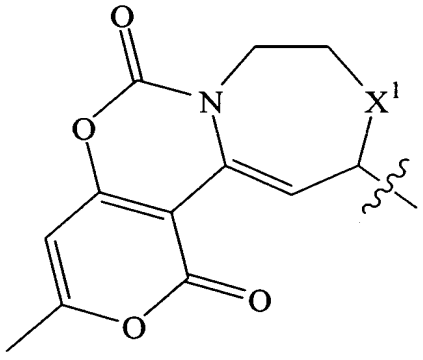
(d)



(e)

in which R^7 is hydrogen or methyl, R^{11} is hydrogen or (C_{1-6})alkyl and the free valance is attached to A^2[, or

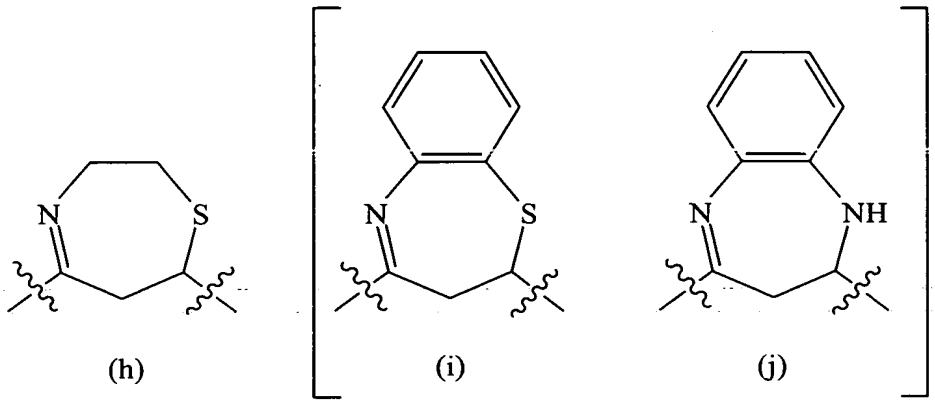
A^2 and A^1 together with R^1 and the atoms to which A^1 and R^1 are attached forms a group of Formula (g):



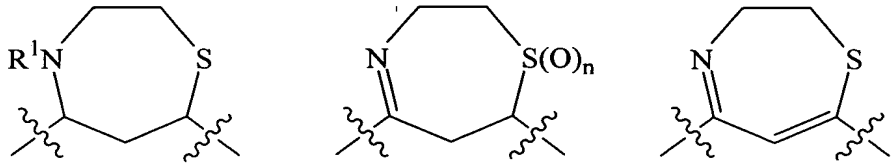
(g)

wherein X^1 is -S- and the free valance is attached to A^{3}]; and

A^2 of said compound is as defined above or is a group selected from Formulae (h), [(i), (j),] (k), (l) and (m):



(h) (i) (j)



(k) (l) (m)

in which n is 1 or 2 and R^1 is acetyl or trifluoroacetyl; or an *N*-oxide derivative, prodrug derivative, protected derivative, individual stereoisomer or mixture of stereoisomers, or a pharmaceutically acceptable salt thereof.

61. The method of Claim 60, wherein A^3 of said compound is phenyl or heteroaryl containing a total of 5 to 9 ring atoms, wherein A^3 may be substituted with a group selected from $-R^{9'}$, $-X^2OR^{9'}$, $-X^2SR^{9'}$ and $-X^2S(O)_2R^{9'}$ [$-R^9$, $-X^2OR^9$, $-X^2SR^9$ and $-X^2S(O)_2R^9$], wherein $R^{9'}$ [R^9] is $-X^2R^{10}$, X^2 is a bond or (C_{1-6})alkylene and R^{10} is phenyl or heteroaryl containing a total of 5 to 6 ring atoms, wherein each ring within A^3 and R^{10} may be substituted with 1 to 3 groups independently selected from (C_{1-6})alkyl, halo, halo-substituted (C_{1-6})alkyl, $-X^2OR^4$, $-X^2SR^4$, $-X^2S(O)_2R^6$ and $-X^2NR^4R^4$, wherein R^4 at each occurrence independently is hydrogen, (C_{1-6})alkyl or halo-substituted (C_{1-6})alkyl and R^6 is (C_{1-6})alkyl or halo-substituted (C_{1-6})alkyl; and the *N*-oxide derivatives, prodrug derivatives, protected derivatives, individual stereoisomers and mixtures of stereoisomers; and the pharmaceutically acceptable salts thereof.

63. The method of claim 57, wherein said compound is selected from the group [list] consisting of:

4-hydroxy-6-methyl-3-[7-(4-methylsulfanyl-phenyl)-2,3,6,7-tetrahydro-[1,4]thiazepin-5-yl]-pyran-2-one;

3-[4-acetyl-7-(2,4-dimethoxy-phenyl)-[1,4]thiazepin [thiazepan]-5-yl]-4-hydroxy-6-methyl-pyran-2-one;

3-[7-(2,4-dimethoxy-phenyl)-4-(2,2,2-trifluoro-ethanoyl)-[1,4] thiazepin [thiazepan]-5-yl]-4-hydroxy-6-methyl-pyran-2-one;

1-[7-(2,4-dimethoxy-phenyl)-5-(3-fluoro-4-methoxyphenyl)-[1,4]thiazepin [thizepan]-4-yl]-ethanone;

4-hydroxy-6-methyl-3-[7-(3-phenyl-1*H*-pyrazol-4-yl)-2,3,6,7-tetrahydro-[1,4]thiazepin-5-yl]-pyran-2-one;

3-[7-(5-ethyl-thien-2-yl)-2,3,6,7-tetrahydro-[1,4]thiazepin-5-yl]-4-hydroxy-6-methyl-pyran-2-one;

3-[7-(1-benzyl-1*H*-indol-3-yl)-2,3,6,7-tetrahydro-[1,4]thiazepin-5-yl]-4-hydroxy-6-methyl-pyran-2-one;

4-hydroxy-6-methyl-3[7-(2-trifluoromethylsulfanyl-phenyl)-2,3,6,7-tetrahydro-[1,4]thiazepin-5-yl]-pyran-2-one;

4-hydroxy-6-methyl-3[7-(3-trifluoromethylsulfanyl-phenyl)-2,3,6,7-tetrahydro-[1,4]thiazepin-5-yl]-pyran-2-one;

4-hydroxy-6-methyl-3[7-(4-trifluoromethylsulfanyl-phenyl)-2,3,6,7-tetrahydro-[1,4]thiazepin-5-yl]-pyran-2-one;

4-hydroxy-6-methyl-3-[7-[3-(3-trifluoromethyl-phenoxy)-phenyl]-2,3,6,7-tetrahydro-[1,4]thiazepin-5-yl]-pyran-2-one;

3-[7-[3-(3,4-dichloro-phenoxy)-phenyl]-2,3,6,7-tetrahydro-[1,4]thiazepin-5-yl]-4-hydroxy-6-methyl-pyran-2-one;

3-[7-[3-(3,5-dichloro-phenoxy)-phenyl]-2,3,6,7-tetrahydro-[1,4]thiazepin-5-yl]-4-hydroxy-6-methyl-pyran-2-one;

4-hydroxy-6-methyl-3-{7-[5-(3-trifluoromethyl-phenyl)-furan-2-yl]-2,3,6,7-tetrahydro-[1,4]thiazepin-5-yl}-pyran-2-one;

3-{7-[5-(2-chloro-phenyl)-furan-2-yl]-2,3,6,7-tetrahydro-[1,4]thiazepin-5-yl}-4-hydroxy-6-methyl-pyran-2-one;

3-{7-[5-(3-chloro-phenyl)-furan-2-yl]-2,3,6,7-tetrahydro-[1,4]thiazepin-5-yl}-4-hydroxy-6-methyl-pyran-2-one;

3-{7-[5-(4-chloro-phenyl)-furan-2-yl]-2,3,6,7-tetrahydro-[1,4]thiazepin-5-yl}-4-hydroxy-6-methyl-pyran-2-one;

4-hydroxy-6-methyl-3-{7-[5-(2-chloro-5-trifluoromethyl-phenyl)-furan-2-yl]-2,3,6,7-tetrahydro-[1,4]thiazepin-5-yl}-pyran-2-one;

3-[7-(4-bromo-thien-2-yl)-2,3,6,7-tetrahydro-[1,4]thiazepin-5-yl]-4-hydroxy-6-methyl-pyran-2-one;

3-[7-(5-bromo-thien-2-yl)-2,3,6,7-tetrahydro-[1,4]thiazepin-5-yl]-4-hydroxy-6-methyl-pyran-2-one;

3-[7-(1-benzenesulfonyl-1*H*-pyrrol-2-yl)-2,3,6,7-tetrahydro-[1,4]thiazepin-5-yl]-4-hydroxy-6-methyl-pyran-2-one;

4-hydroxy-6-methyl-3-[7-(3-methyl-thien-2-yl)-2,3,6,7-tetrahydro-[1,4]thiazepin-5-yl]-pyran-2-one;

4-hydroxy-6-methyl-3-[7-(5-methyl-thien-2-yl)-2,3,6,7-tetrahydro-[1,4]thiazepin-5-yl]-pyran-2-one;

4-hydroxy-6-methyl-3-[7-(1-methyl-1*H*-indol-3-yl)-2,3,6,7-tetrahydro-[1,4]thiazepin-5-yl]-pyran-2-one;

3-[7-(3-chloro-2-methyl-5-trifluoromethyl-1*H*-pyrazol-4-yl)-2,3,6,7-tetrahydro-[1,4]thiazepin-5-yl]-4-hydroxy-6-methyl-pyran-2-one;

3-{7-[1-(2,4-difluoro-benzenesulfonyl)-1*H*-pyrrrol-2-yl]-2,3,6,7-tetrahydro-[1,4]thiazepin-5-yl}-4-hydroxy-6-methyl-pyran-2-one;

3-(7-[2,2′]bithienyl-5-yl-2,3,6,7-tetrahydro-[1,4]thiazepin-5-yl)-4-hydroxy-6-methyl-pyran-2-one;

3-{7-[1-(3,5-dichloro-phenyl)-1*H*-pyrrrol-2-yl]-2,3,6,7-tetrahydro-[1,4]thiazepin-5-yl}-4-hydroxy-6-methyl-pyran-2-one;

3-{7-[1-(4-chloro-phenyl)-1*H*-pyrrrol-2-yl]-2,3,6,7-tetrahydro-[1,4]thiazepin-5-yl}-4-hydroxy-6-methyl-pyran-2-one;

3-[7-(5-chloro-1*H*-indol-3-yl)-2,3,6,7-tetrahydro-[1,4]thiazepin-5-yl]-4-hydroxy-6-methyl-pyran-2-one;

[4-hydroxy-6-methyl-3-[7-(6-*p*-tolylsulfanyl-imidazo[2,1-*b*]thiazol-5-yl)-2,3,6,7-tetrahydro-[1,4]thiazepin-5-yl]-pyran-2-one;]

3-[7-(4,5-dibromo-thien-2-yl)-2,3,6,7-tetrahydro-[1,4]thiazepin-5-yl]-4-hydroxy-6-methyl-pyran-2-one;

3-[7-(2-chloro-5-trifluoromethyl-phenyl)-2,3,6,7-tetrahydro-[1,4]thiazepin-5-yl]-4-hydroxy-6-methyl-pyran-2-one;

3-[7-(2,4-dimethoxy-phenyl)-2,3,6,7-tetrahydro-[1,4]thiazepin-5-yl]-4-hydroxy-6-methyl-5,6-dihydro-pyran-2-one;

4-hydroxy-6-methyl-3-[7-(5-methylsulfanyl-thien-2-yl)-2,3,6,7-tetrahydro-[1,4]thiazepin-5-yl]-pyran-2-one;

3-[7-(5-chloro-1-methyl-3-phenyl-1*H*-pyrazol-4-yl)-2,3,6,7-tetrahydro-[1,4]thiazepin-5-yl]-4-hydroxy-6-methyl-pyran-2-one;

[3-[4-(2,4-dimethoxy-phenyl)-4,5-dihydro-3*H*-benzo[*b*][1,4]diazepin-2-yl]-4-hydroxy-6-methyl-pyran-2-one;]

3-[7-(4-dimethylamino-phenyl)-2,3,6,7-tetrahydro-[1,4]thiazepin-5-yl]-4-hydroxy-6-methyl-pyran-2-one;

3-[7-(2,4-dimethoxy-phenyl)-2,3,6,[,]7-tetrahydro-[1,4]thiazepin-5-yl]-4-hydroxy-1*H*-quinolin-2-one;

4-hydroxy-6-methyl-3-[7-(4-trifluoromethoxy-phenyl)-2,3,6,7-tetrahydro-[1,4]thiazepin-5-yl]-pyran-2-one;

3-[7-(bis-trifluoromethyl-phenyl)-2,3,6,7-tetrahydro-[1,4]thiazepin-5-yl]-4-hydroxy-6-methyl-pyran-2-one;

3-[7-(4-dimethylamino-2-methoxy-phenyl)-2,3,6,7-tetrahydro-[1,4]thiazepin-5-yl]-4-hydroxy-6-methyl-pyran-2-one;

[3-hydroxy-2-[2-(2,4-diethoxy-phenyl)-2,3-dihydro-benzo[*b*][1,4]thiazepin-4-yl]-cyclohex-2-enone;]

3-[7-(2,4-dimethoxy-phenyl)-1-oxo-2,3,6,7-tetrahydro-1*H*-1λ^4-[1,4]thiazepin-5-yl]-4-hydroxy-6-methoxy-pyran-2-one;

[10-(2,4-dimethoxy-phenyl)-3-methyl-7,8-dihydro-10*H*-2,5-dioxa-9-thia-6a-aza-cyclohepta[*a*]naphthalene-1,6-dione;]

3-[7-(2,4-dimethoxy-phenyl)-1,1-dioxo-2,3,6,7-tetrahydro-1*H*-1λ^6-[1,4]thiazepin-5-yl]-4-hydroxy-6-methyl-pyran-2-one;

3-[7-(2,4-diethoxy-phenyl)-2,3-dihydro-[1,4]thiazepin-5-yl]-4-hydroxy-6-methyl-pyran-2-one;

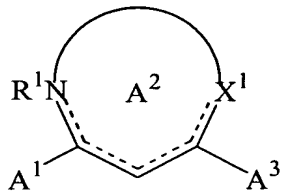
3-(7-[2,2′]bithienyl-5-yl-2,3-dihydro-[1,4]thiazepin-5-yl)-4-hydroxy-6-methyl-pyran-2-one;

2-[7-(2,4-diethoxy-phenyl)-2,3-dihydro-[1,4]thiazepin-5-yl]-3-hydroxy-cyclohex-2-enone; and

3-[7-(2,4-diethoxy-phenyl)-2,3-dihydro-[1,4]thiazepin-5-yl]-4-hydroxy-6-methyl-5,6-dihydro-pyran-2-one; or

a *N*-oxide derivative, derivative, protected derivative, individual stereoisomer or mixture of stereoisomers; or a pharmaceutically acceptable salt thereof.

66. A method for treating [or preventing] cancer, comprising administering to an animal in need of such treatment an effective amount of a compound of Formula I:



I

in which:

the dashed lines indicate optional unsaturation without violating valency rules;

R^1 is hydrogen, (C_{1-6})alkyl or $-C(O)R^6$, wherein R^6 is as defined below, or R^1 is absent when a double bond exists between the nitrogen atom to which R^1 is attached and an adjacent ring atom or R^1 is as defined below;

X^1 is $-S(O)_n-$, wherein n is 0, 1, or 2 [$-NR^2-$, -S-, -S(O)-, $-S(O)_2-$ or -O-, wherein R^2 is hydrogen or (C_{1-6})alkyl or is absent when a double bond exists between the nitrogen atom to which R^2 is attached and an adjacent ring atom];

A^1 is a monocyclic or fused polycyclic ring system selected from aryl containing a total of 6 to 14 ring atoms, heteroaryl containing a total of 5 to 14 ring atoms and

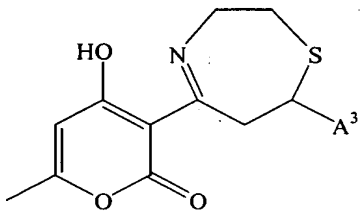
unsaturated, partially unsaturated or saturated carbocycloalkyl or heterocycloalkyl each containing a total of 3 to 14 ring atoms, [or A^1 together with R^1 and the atoms to which A^1 and R^1 are attached forms a fused polycyclic ring system selected from heteroaryl and unsaturated, partially unsaturated or saturated heterocycloalkyl in any case containing a total of 10 to 15 ring atoms,] wherein A^1 may be substituted with a group selected from $-R^3$, $-X^2OR^3$, $-X^2C(O)R^3$, $-X^2OC(O)R^3$, $-X^2C(O)OR^3$, $-X^2SR^3$, $-X^2S(O)R^3$, $-X^2S(O)_2R^3$, $-X^2NR^3R^4$, $-X^2NR^4C(O)R^3$, $-X^2NR^4C(O)OR^3$, $-X^2C(O)NR^3R^4$, $-X^2NR^4C(O)NR^3R^4$, $-X^2NR^4C(NR^4)NR^3R^4$, $-X^2NR^4S(O)_2R^3$ and $-X^2S(O)_2NR^3R^4$, wherein X^2 is a bond or (C_{1-6})alkylene, R^3 is $-X^2R^5$ wherein X^2 is as defined above and R^5 is aryl containing a total of 6 to 10 ring atoms, heteroaryl containing a total of 5 to 10 ring atoms or unsaturated, partially unsaturated or saturated carbocycloalkyl or heterocycloalkyl each containing a total of 3 to 10 ring atoms, and R^4 at each occurrence independently is hydrogen, (C_{1-6})alkyl or halo-substituted (C_{1-6})alkyl, wherein each ring within A^1 and R^5 that contains from 3 to 8 ring atoms [and] may be substituted with 1 to 3 groups independently selected from (C_{1-6})alkyl, cyano, halo, nitro, halo-substituted (C_{1-6})alkyl, $-X^2OR^4$, $-X^2C(O)R^6$, $-X^2OC(O)R^6$, $-X^2C(O)OR^4$, $-X^2SR^4$, $-X^2S(O)R^6$, $-X^2S(O)_2R^6$, $-X^2NR^4R^4$, $-X^2NR^4C(O)R^6$, $-X^2NR^4C(O)OR^4$, $-X^2C(O)NR^4R^4$, $-X^2NR^4C(O)NR^4R^4$, $-X^2NR^4C(NR^4)NR^4R^4$, $-X^2NR^4S(O)_2R^6$ and $-X^2S(O)_2NR^4R^4$, wherein X^2 and R^4 are as defined above and R^6 is (C_{1-6})alkyl or halo-substituted (C_{1-6})alkyl, and wherein any said carbocycloalkyl and heterocycloalkyl rings within A^1 and R^5 may be substituted further with 1 to 2 groups independently selected from (C_{1-6})alkylidene, oxo, imino and thioxo, with the provisos that only one of A^1 and R^5 is a fused polycyclic ring system;

A^2 is a monocyclic [or fused bicyclic] ring selected from heteroarylene or unsaturated, partially unsaturated or saturated heterocycloalkylene containing a total of 5 to 11 ring atoms, wherein A^2 may be substituted with a group selected from $-R^8$, $-X^2OR^8$, $-X^2C(O)R^8$, $-X^2OC(O)R^8$, $-X^2C(O)OR^8$, $-X^2SR^8$, $-X^2S(O)R^8$, $-X^2S(O)_2R^8$, $-X^2NR^4R^8$, $-X^2NR^4C(O)R^8$, $-X^2NR^4C(O)OR^8$, $-X^2C(O)NR^4R^8$, $-X^2NR^4C(O)NR^4R^8$, $-X^2NR^4C(NR^4)NR^4R^8$, $-X^2NR^4S(O)_2R^8$ and $-X^2S(O)_2NR^4R^8$, wherein X^2 is a bond or (C_{1-6})alkylene, R^8 is $-X^2R^9$ wherein X^2 is as defined above and R^9 is aryl containing a total of 6 to 10 ring atoms, heteroaryl containing a total of 5 to 10 ring atoms or unsaturated, partially unsaturated or saturated carbocycloalkyl or heterocycloalkyl each containing a total

of 3 to 10 ring atoms, and R^4 at each occurrence independently is hydrogen, (C_{1-6})alkyl or halo-substituted (C_{1-6})alkyl, wherein each ring within A^2 and R^8 that contains from 3 to 8 ring atoms [and] may be substituted with 1 to 3 groups independently selected from (C_{1-6})alkyl, cyano, halo, nitro, halo-substituted (C_{1-6})alkyl, $-X^2OR^4$, $-X^2C(O)R^6$, $-X^2OC(O)R^6$, $-X^2C(O)OR^4$, $-X^2SR^4$, $-X^2S(O)R^6$, $-X^2S(O)_2R^6$, $-X^2NR^4R^4$, $-X^2NR^4C(O)R^6$, $-X^2NR^4C(O)OR^4$, $-X^2C(O)NR^4R^4$, $-X^2NR^4C(O)NR^4R^4$, $-X^2NR^4C(NR^4)NR^4R^4$, $-X^2C(O)NR^4X^2C(O)OR^4$, $-X^2NR^4S(O)_2R^6$ and $-X^2S(O)_2NR^4R^4$, wherein X^2 and R^4 are as defined above and R^6 is (C_{1-6})alkyl or halo-substituted (C_{1-6})alkyl, and wherein any said heterocycloalkylene, carbocycloalkyl and heterocycloalkyl rings within A^2 and R^8 may be substituted further with 1 to 2 groups independently selected from (C_{1-6})alkylidene, oxo, imino and thioxo, with the proviso that only one of A^2 and R^8 is a fused polycyclic ring system; and

A^3 is a monocyclic or fused polycyclic ring system selected from aryl containing a total of 6 to 14 ring atoms, heteroaryl containing a total of 5 to 14 ring atoms and unsaturated, partially unsaturated or saturated carbocycloalkyl or heterocycloalkyl each containing a total of 3 to 14 ring atoms, wherein A^3 may be substituted with a group selected from $-R^{9'}$, $-X^2OR^{9'}$, $-X^2C(O)R^{9'}$, $-X^2OC(O)R^{9'}$, $-X^2C(O)OR^{9'}$, $-X^2SR^{9'}$, $-X^2S(O)R^{9'}$, $-X^2S(O)_2R^{9'}$, $-X^2NR^4R^{9'}$, $-X^2NR^4C(O)R^{9'}$, $-X^2NR^4C(O)OR^{9'}$, $-X^2C(O)NR^4R^{9'}$, $-X^2NR^4C(O)NR^4R^{9'}$, $-X^2NR^4C(NR^4)NR^4R^{9'}$, $-X^2NR^4S(O)_2R^{9'}$ and $-X^2S(O)_2NR^4R^{9'}$ [$-R^9$, $-X^2OR^9$, $-X^2C(O)R^9$, $-X^2OC(O)R^9$, $-X^2C(O)OR^9$, $-X^2SR^9$, $-X^2S(O)R^9$, $-X^2S(O)_2R^9$, $-X^2NR^4R^9$, $-X^2NR^4C(O)R^9$, $-X^2NR^4C(O)OR^9$, $-X^2C(O)NR^4R^9$, $-X^2NR^4C(O)NR^4R^9$, $-X^2NR^4C(NR^4)NR^4R^9$, $-X^2NR^4S(O)_2R^9$ and $-X^2S(O)_2NR^4R^9$], wherein X^2 is a bond or (C_{1-6})alkylene, $R^{9'}$ [R^9] is $-X^2R^{10}$ wherein X^2 is as defined above and R^{10} is aryl containing a total of 6 to 10 ring atoms, heteroaryl containing a total of 5 to 10 ring atoms or unsaturated, partially unsaturated or saturated carbocycloalkyl or heterocycloalkyl each containing a total of 3 to 10 ring atoms, and R^4 at each occurrence independently is hydrogen, (C_{1-6})alkyl or halo-substituted (C_{1-6})alkyl, wherein each ring within A^3 and R^{10} that contains from 3 to 8 ring atoms [and] may be substituted with 1 to 3 groups independently selected from (C_{1-6})alkyl, cyano, halo, nitro, halo-substituted (C_{1-6})alkyl, $-X^2OR^4$, $-X^2C(O)R^6$, $-X^2OC(O)R^6$, $-X^2C(O)OR^4$, $-X^2SR^4$, $-X^2S(O)R^6$, $-X^2S(O)_2R^6$, $-X^2NR^4R^4$, $-X^2NR^4C(O)R^6$, $-X^2NR^4C(O)OR^4$, $-X^2C(O)NR^4R^4$, $-X^2NR^4C(O)NR^4R^4$, $-X^2NR^4C(NR^4)NR^4R^4$, $-X^2NR^4S(O)_2R^6$ and $-X^2S(O)_2NR^4R^4$, wherein X^2 and R^4 are as defined above and R^6 is

(C_{1-6})alkyl or halo-substituted (C_{1-6})alkyl, and wherein any said carbocycloalkyl and heterocycloalkyl rings within A^3 and R^{10} may be substituted further with 1 to 2 groups independently selected from (C_{1-6})alkylidene, oxo, imino and thioxo, with the proviso that only one of A^3 and R^{10} is a fused polycyclic ring system; or an *N*-oxide derivative, prodrug derivative, protected derivative, individual stereoisomer or mixture of stereoisomers, or a pharmaceutically acceptable salt thereof; with the proviso that when said compound is of Formula II(a):



II(a)

then A^3 is other than:

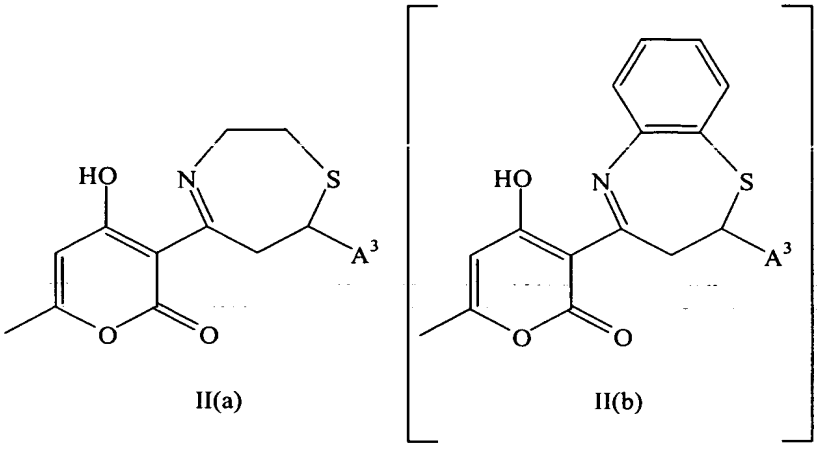
(a) benzo[1,3]dioxolyl;

(b) phenyl which is mono-substituted by bromo, hydroxy, methyl or isopropyl; and

(c) phenyl which is substituted by at least one of Cl and methoxy and not substituted by methylsulfanyl, amino, methylamino and dimethylamino; or

a *N*-oxide derivative, prodrug derivative, protected derivative, individual stereoisomer or mixture of stereoisomers; or a pharmaceutically acceptable salt thereof.

67. The method of claim 66, with the further proviso that when said compound is [selected the group consisting of] Formula II(a) [and II(b)]:



II(a) II(b)

then A^3 is other than:

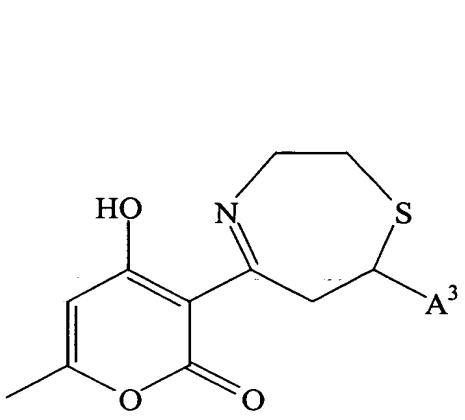
(a) benzo[1,3]dioxolyl;

(b) phenyl which is mono-substituted by bromo, nitro, hydroxy, methyl, or isopropyl; and

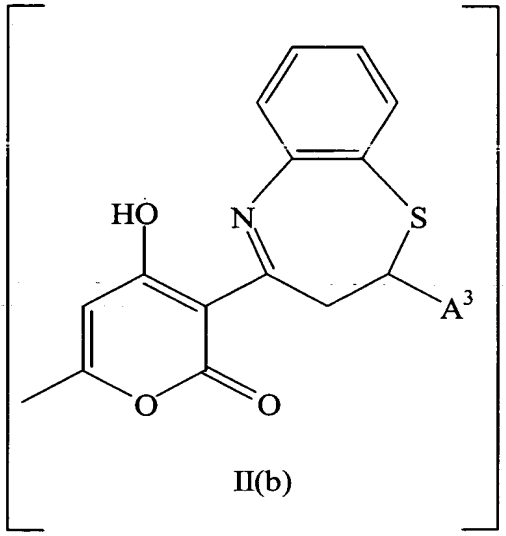
(c) phenyl which is substituted by at least one of Cl and methoxy and not substituted by methylsulfanyl, amino, methylamino and dimethylamino; or

a *N*-oxide derivative, derivative, protected derivative, individual stereoisomer or mixture of stereoisomers; or a pharmaceutically acceptable salt thereof.

68. The method of claim 66, with the further proviso that when said compound is [selected the group consisting of] Formula II(a) [and II(b)]:



II(a)



II(b)

then A^3 is other than:

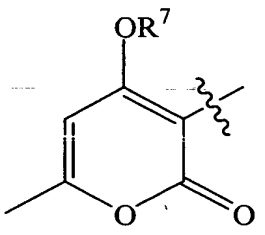
(a) benzo[1,3]dioxolyl;

(b) 2,3-dihydro-benzo[1,4]dioxinyl; and

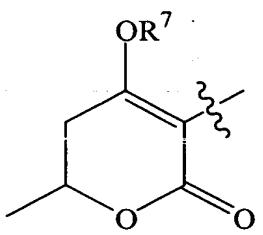
(c) phenyl which is substituted by at least one of bromo, chloro, hydroxy, nitro, methoxy and (C_{1-3})alkyl; or

a *N*-oxide derivative, derivative, protected derivative, individual stereoisomer or mixture of stereoisomers; or a pharmaceutically acceptable salt thereof.[.]

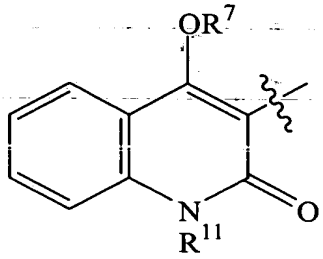
69. The method of Claim 66, wherein A^1 of said compound is a group selected from Formulae (a), (b), (c), (d) and (e):



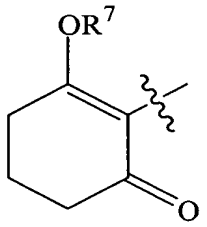
(a)



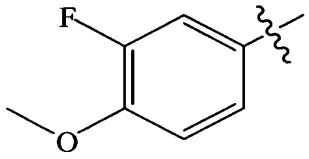
(b)



(c)



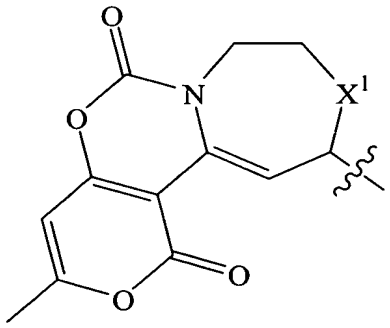
(d)



(e)

in which R^7 is hydrogen or methyl, R^{11} is hydrogen or (C_{1-6})alkyl and the free valance is attached to A^2[, or

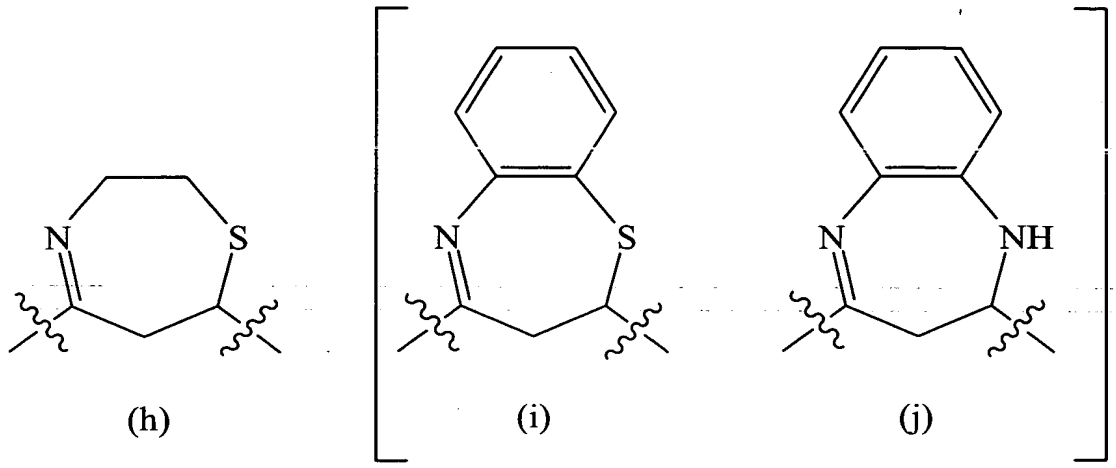
A^2 and A^1 together with R^1 and the atoms to which A^1 and R^1 are attached forms a group of Formula (g):



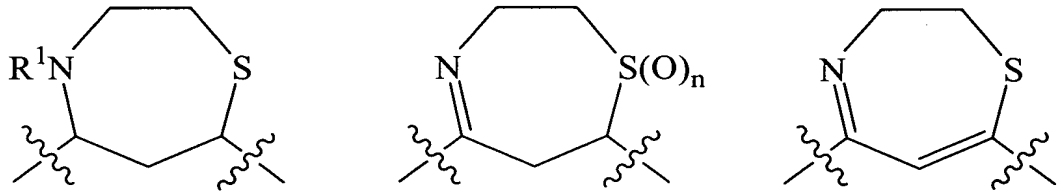
(g)

wherein X^1 is -S- and the free valance is attached to A^3]; and

A^2 of said compound is as defined above or is a group selected from Formulae (h), [(i), (j),] (k), (l) and (m):



(h) (i) (j)



(k) (l) (m)

in which n is 1 or 2 and R^1 is acetyl or trifluoroacetyl; or a *N*-oxide derivative, prodrug derivative, protected derivative, individual stereoisomer or mixture of stereoisomers; or a pharmaceutically acceptable salt thereof.

70. The method of Claim 69, wherein A^3 of said compound is phenyl or heteroaryl containing a total of 5 to 9 ring atoms, wherein A^3 may be substituted with a group selected from $\underline{-R^{9'}, -X^2OR^{9'}, -X^2SR^{9'} \text{ and } -X^2S(O)_2R^{9'}}$ [$-R^9$, $-X^2OR^9$, $-X^2SR^9$ and $-X^2S(O)_2R^9$], wherein $\underline{R^{9'}}$ [R^9] is $-X^2R^{10}$, X^2 is a bond or (C_{1-6})alkylene and R^{10} is phenyl or heteroaryl containing a total of 5 to 6 ring atoms, wherein each ring within A^3 and R^{10} may be substituted with 1 to 3 groups independently selected from (C_{1-6})alkyl, halo, halo-substituted (C_{1-6})alkyl, $-X^2OR^4$, $-X^2SR^4$, $-X^2S(O)_2R^6$ and $-X^2NR^4R^4$, wherein R^4 at each occurrence independently is hydrogen, (C_{1-6})alkyl or halo-substituted (C_{1-6})alkyl and R^6 is (C_{1-6})alkyl or halo-substituted (C_{1-6})alkyl; or a *N*-oxide derivative, prodrug derivative, protected derivative, individual stereoisomer or mixture of stereoisomers; or a pharmaceutically acceptable salt thereof.

72. The method of claim 66, wherein said compound is selected from the group [list] consisting of:

3-[4-acetyl-7-(2,4-dimethoxy-phenyl)-[1,4]thiazepin [thiazepan]-5-yl]-4-hydroxy-6-methyl-pyran-2-one;

3-[7-(2,4-dimethoxy-phenyl)-4-(2,2,2-trifluoro-ethanoyl)-[1,4]thiazepin [thiazepan]-5-yl]-4-hydroxy-6-methyl-pyran-2-one;

1-[7-(2,4-dimethoxy-phenyl)-5-(3-fluoro-4-methoxyphenyl)-[1,4]thiazepin [thizepan]-4-yl]-ethanone;

4-hydroxy-6-methyl-3-[7-(3-phenyl-1*H*-pyrazol-4-yl)-2,3,6,7-tetrahydro-[1,4]thiazepin-5-yl]-pyran-2-one;

3-[7-(5-ethyl-thien-2-yl)-2,3,6,7-tetrahydro-[1,4]thiazepin-5-yl]-4-hydroxy-6-methyl-pyran-2-one;

3-[7-(1-benzyl-1*H*-indol-3-yl)-2,3,6,7-tetrahydro-[1,4]thiazepin-5-yl]-4-hydroxy-6-methyl-pyran-2-one;

4-hydroxy-6-methyl-3[7-(2-trifluoromethylsulfanyl-phenyl)-2,3,6,7-tetrahydro-[1,4]thiazepin-5-yl]-pyran-2-one;

4-hydroxy-6-methyl-3[7-(3-trifluoromethylsulfanyl-phenyl)-2,3,6,7-tetrahydro-[1,4]thiazepin-5-yl]-pyran-2-one;

4-hydroxy-6-methyl-3[7-(4-trifluoromethylsulfanyl-phenyl)-2,3,6,7-tetrahydro-[1,4]thiazepin-5-yl]-pyran-2-one;

4-hydroxy-6-methyl-3-[7-[3-(3-trifluoromethyl-phenoxy)-phenyl]-2,3,6,7-tetrahydro-[1,4]thiazepin-5-yl]-pyran-2-one;

3-[7-[3-(3,4-dichloro-phenoxy)-phenyl]-2,3,6,7-tetrahydro-[1,4]thiazepin-5-yl]-4-hydroxy-6-methyl-pyran-2-one;

3-[7-[3-(3,5-dichloro-phenoxy)-phenyl]-2,3,6,7-tetrahydro-[1,4]thiazepin-5-yl]-4-hydroxy-6-methyl-pyran-2-one;

4-hydroxy-6-methyl-3-{7-[5-(3-trifluoromethyl-phenyl)-furan-2-yl]-2,3,6,7-tetrahydro-[1,4]thiazepin-5-yl}-pyran-2-one;

3-{7-[5-(2-chloro-phenyl)-furan-2-yl]-2,3,6,7-tetrahydro-[1,4]thiazepin-5-yl}-4-hydroxy-6-methyl-pyran-2-one;

3-{7-[5-(3-chloro-phenyl)-furan-2-yl]-2,3,6,7-tetrahydro-[1,4]thiazepin-5-yl}-4-hydroxy-6-methyl-pyran-2-one;

3-{7-[5-(4-chloro-phenyl)-furan-2-yl]-2,3,6,7-tetrahydro-[1,4]thiazepin-5-yl}-4-hydroxy-6-methyl-pyran-2-one;

4-hydroxy-6-methyl-3-{7-[5-(2-chloro-5-trifluoromethyl-phenyl)-furan-2-yl]-2,3,6,7-tetrahydro-[1,4]thiazepin-5-yl}-pyran-2-one;

3-[7-(4-bromo-thien-2-yl)-2,3,6,7-tetrahydro-[1,4]thiazepin-5-yl]-4-hydroxy-6-methyl-pyran-2-one;

3-[7-(5-bromo-thien-2-yl)-2,3,6,7-tetrahydro-[1,4]thiazepin-5-yl]-4-hydroxy-6-methyl-pyran-2-one;

3-[7-(1-benzenesulfonyl-1*H*-pyrrol-2-yl)-2,3,6,7-tetrahydro-[1,4]thiazepin-5-yl]-4-hydroxy-6-methyl-pyran-2-one;

4-hydroxy-6-methyl-3-[7-(3-methyl-thien-2-yl)-2,3,6,7-tetrahydro-[1,4]thiazepin-5-yl]-pyran-2-one;

4-hydroxy-6-methyl-3-[7-(5-methyl-thien-2-yl)-2,3,6,7-tetrahydro-[1,4]thiazepin-5-yl]-pyran-2-one;

4-hydroxy-6-methyl-3-[7-(1-methyl-1*H*-indol-3-yl)-2,3,6,7-tetrahydro-[1,4]thiazepin-5-yl]-pyran-2-one;

3-[7-(3-chloro-2-methyl-5-trifluoromethyl-1*H*-pyrazol-4-yl)-2,3,6,7-tetrahydro-[1,4]thiazepin-5-yl]-4-hydroxy-6-methyl-pyran-2-one;

3-{7-[1-(2,4-difluoro-benzenesulfonyl)-1*H*-pyrrrol-2-yl]-2,3,6,7-tetrahydro-[1,4]thiazepin-5-yl}-4-hydroxy-6-methyl-pyran-2-one;

3-(7-[2,2′]bithienyl-5-yl-2,3,6,7-tetrahydro-[1,4]thiazepin-5-yl)-4-hydroxy-6-methyl-pyran-2-one;

3-{7-[1-(3,5-dichloro-phenyl)-1*H*-pyrrrol-2-yl]-2,3,6,7-tetrahydro-[1,4]thiazepin-5-yl}-4-hydroxy-6-methyl-pyran-2-one;

3-{7-[1-(4-chloro-phenyl)-1*H*-pyrrrol-2-yl]-2,3,6,7-tetrahydro-[1,4]thiazepin-5-yl}-4-hydroxy-6-methyl-pyran-2-one;

3-[7-(5-chloro-1*H*-indol-3-yl)-2,3,6,7-tetrahydro-[1,4]thiazepin-5-yl]-4-hydroxy-6-methyl-pyran-2-one;

[4-hydroxy-6-methyl-3-[7-(6-*p*-tolylsulfanyl-imidazo[2,1-*b*]thiazol-5-yl)-2,3,6,7-tetrahydro-[1,4]thiazepin-5-yl]-pyran-2-one;]

3-[7-(4,5-dibromo-thien-2-yl)-2,3,6,7-tetrahydro-[1,4]thiazepin-5-yl]-4-hydroxy-6-methyl-pyran-2-one;

3-[7-(2-chloro-5-trifluoromethyl-phenyl)-2,3,6,7-tetrahydro-[1,4]thiazepin-5-yl]-4-hydroxy-6-methyl-pyran-2-one;

3-[7-(2,4-dimethoxy-phenyl)-2,3,6,7-tetrahydro-[1,4]thiazepin-5-yl]-4-hydroxy-6-methyl-5,6-dihydro-pyran-2-one;

4-hydroxy-6-methyl-3-[7-(5-methylsulfanyl-thien-2-yl)-2,3,6,7-tetrahydro-[1,4]thiazepin-5-yl]-pyran-2-one;

3-[7-(5-chloro-1-methyl-3-phenyl-1*H*-pyrazol-4-yl)-2,3,6,7-tetrahydro-[1,4]thiazepin-5-yl]-4-hydroxy-6-methyl-pyran-2-one;

[3-[4-(2,4-dimethoxy-phenyl)-4,5-dihydro-3*H*-benzo[*b*][1,4]diazepin-2-yl]-4-hydroxy-6-methyl-pyran-2-one;]

3-[7-(4-dimethylamino-phenyl)-2,3,6,7-tetrahydro-[1,4]thiazepin-5-yl]-4-hydroxy-6-methyl-pyran-2-one;

3-[7-(2,4-dimethoxy-phenyl)-2,3,6,[,]7-tetrahydro-[1,4]thiazepin-5-yl]-4-hydroxy-1*H*-quinolin-2-one;

4-hydroxy-6-methyl-3-[7-(4-trifluoromethoxy-phenyl)-2,3,6,7-tetrahydro-[1,4]thiazepin-5-yl]-pyran-2-one;

3-[7-(bis-trifluoromethyl-phenyl)-2,3,6,7-tetrahydro-[1,4]thiazepin-5-yl]-4-hydroxy-6-methyl-pyran-2-one;

3-[7-(4-dimethylamino-2-methoxy-phenyl)-2,3,6,7-tetrahydro-[1,4]thiazepin-5-yl]-4-hydroxy-6-methyl-pyran-2-one;

[3-hydroxy-2-[2-(2,4-diethoxy-phenyl)-2,3-dihydro-benzo[*b*][1,4]thiazepin-4-yl]-cyclohex-2-enone;]

3-[7-(2,4-dimethoxy-phenyl)-1-oxo-2,3,6,7-tetrahydro-1*H*-1λ^4-[1,4]thiazepin-5-yl]-4-hydroxy-6-methoxy-pyran-2-one;

[10-(2,4-dimethoxy-phenyl)-3-methyl-7,8-dihydro-10*H*-2,5-dioxa-9-thia-6a-aza-cyclohepta[*a*]naphthalene-1,6-dione;]

3-[7-(2,4-dimethoxy-phenyl)-1,1-dioxo-2,3,6,7-tetrahydro-1*H*-1λ^6-[1,4]thiazepin-5-yl]-4-hydroxy-6-methyl-pyran-2-one;

3-[7-(2,4-diethoxy-phenyl)-2,3-dihydro-[1,4]thiazepin-5-yl]-4-hydroxy-6-methyl-pyran-2-one;

3-(7-[2,2′]bithienyl-5-yl-2,3-dihydro-[1,4]thiazepin-5-yl)-4-hydroxy-6-methyl-pyran-2-one;

2-[7-(2,4-diethoxy-phenyl)-2,3-dihydro-[1,4]thiazepin-5-yl]-3-hydroxy-cyclohex-2-enone; and

3-[7-(2,4-diethoxy-phenyl)-2,3-dihydro-[1,4]thiazepin-5-yl]-4-hydroxy-6-methyl-5,6-dihydro-pyran-2-one; or

a *N*-oxide derivative, prodrug derivative, protected derivative, individual stereoisomer or mixture of stereoisomers; or a pharmaceutically acceptable salt thereof.

73. A method for treating [or preventing] cancer, comprising administering to an animal in need of such treatment an effective amount of a compound selected from the group consisting of:

4-hydroxy-6-methyl-3-[7-(4-methylsulfanyl-phenyl)-2,3,6,7-tetrahydro-[1,4]thiazepin-5-yl]-pyran-2-one;

3-[7-(4-ethoxy-phenyl)-2,3,6,7-tetrahydro-[1,4]thiazepin-5-yl]-4-hydroxy-6-methyl-pyran-2-one;

3-[7-(3-methoxy-phenyl)-2,3,6,7-tetrahydro-[1,4]thiazepin-5-yl]-6-methyl-pyran-2-one;

3-[7-(2-bromo-phenyl)-2,3,6,7-tetrahydro-[1,4]thiazepin-5-yl]-4-hydroxy-6-methyl-pyran-2-one;

3-[7-(2,3-dichloro-phenyl)-2,3,6,7-tetrahydro-[1,4]thiazepin-5-yl]-4-hydroxy-6-methyl-pyran-2-one;

3-[7-(3,4-dichloro-phenyl)-2,3,6,7-tetrahydro-[1,4]thiazepin-5-yl]-4-hydroxy-6-methyl-pyran-2-one;

6-methyl-3-[7-(2,3,4-trimethoxy-phenyl)-2,3,6,7-tetrahydro-[1,4]thiazepin-5-yl]-pyran-2-one;

[6-methyl-3-(2-*p*-tolyl-2,3-dihydro-benzo[*b*][1,4]thiazepin-4-yl)-pyran-2-one;

4-hydroxy-6-methyl-3-[2-(4-methylsulfanyl-phenyl)-2,3-dihydro-benzo[*b*][1,4]thiazepin-4-yl]-pyran-2-one;]

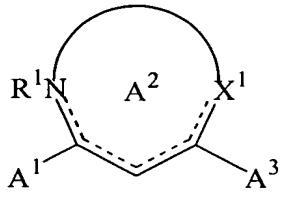
4-hydroxy-3-[7-(4-chloro-2-methoxy-phenyl)-2,3,6,7-tetrahydro-[1,4]thiazepin-5-yl]-6-methyl-pyran-2-one; and

4-hydroxy-3-[7-(2,4-diethoxy-phenyl)-2,3,6,7-tetrahydro-[1,4]thiazepin-5-yl]-6-methyl-pyran-2-one; or

a *N*-oxide derivative, prodrug derivative, protected derivative, individual stereoisomer or mixture of stereoisomers; or a pharmaceutically acceptable salt thereof.

75. The method of Claims 66 or [and] 73, wherein said cancer is selected from the group consisting of Hodgkin's disease, non-Hodgkin's lymphoma, acute and chronic lymphocytic leukemias, multiple myeloma, neuroblastoma, breast carcinoma, ovarian carcinoma, lung carcinoma, Wilms' tumor, cervical carcinoma, testicular carcinoma, soft-tissue sarcoma, chronic lymphocytic leukemia, primary macroglobulinemia, bladder carcinoma, chronic granulocytic leukemia, primary brain carcinoma, malignant melanoma, small-cell lung carcinoma, stomach carcinoma, colon carcinoma, malignant pancreatic insulinoma, malignant carcinoid carcinoma, choriocarcinoma, mycosis fungoides, head and neck carcinoma, osteogenic sarcoma, pancreatic carcinoma, acute granulocytic leukemia, hairy cell leukemia, [neuroblastoma,] rhabdomyosarcoma, Kaposi's sarcoma, genitourinary carcinoma, thyroid carcinoma, esophageal carcinoma, malignant hypercalcemia, cervical hyperplasia, renal cell carcinoma, endometrial carcinoma, polycythemia vera, essential thrombocytosis, adrenal cortex carcinoma, skin cancer and [an] prostatic carcinoma.

76. A method for the treatment of drug resistant cancer, comprising administering to an animal in need of such treatment an effective amount of a compound of compound of Formula I:



I

in which:

the dashed lines indicate optional unsaturation without violating valency rules;

R^1 is hydrogen, (C_{1-6})alkyl or $-C(O)R^6$, wherein R^6 is as defined below, or R^1 is absent when a double bond exists between the nitrogen atom to which R^1 is attached and an adjacent ring atom or R^1 is as defined below;

X^1 is $-S(O)_n-$, wherein n is 0, 1, or 2 [$-NR^2-$, $-S-$, $-S(O)-$, $-S(O)_2-$ or $-O-$, wherein R^2 is hydrogen or (C_{1-6})alkyl or is absent when a double bond exists between the nitrogen atom to which R^2 is attached and an adjacent ring atom];

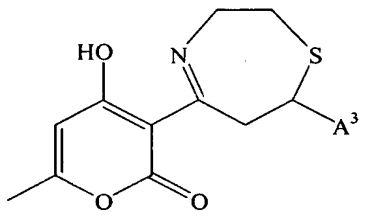
A^1 is a monocyclic or fused polycyclic ring system selected from aryl containing a total of 6 to 14 ring atoms, heteroaryl containing a total of 5 to 14 ring atoms and unsaturated, partially unsaturated or saturated carbocycloalkyl or heterocycloalkyl each containing a total of 3 to 14 ring atoms, [or A^1 together with R^1 and the atoms to which A^1 and R^1 are attached forms a fused polycyclic ring system selected from heteroaryl and unsaturated, partially unsaturated or saturated heterocycloalkyl in any case containing a total of 10 to 15 ring atoms,] wherein A^1 may be substituted with a group selected from $-R^3$, $-X^2OR^3$, $-X^2C(O)R^3$, $-X^2OC(O)R^3$, $-X^2C(O)OR^3$, $-X^2SR^3$, $-X^2S(O)R^3$, $-X^2S(O)_2R^3$, $-X^2NR^3R^4$, $-X^2NR^4C(O)R^3$, $-X^2NR^4C(O)OR^3$, $-X^2C(O)NR^3R^4$, $-X^2NR^4C(O)NR^3R^4$, $-X^2NR^4C(NR^4)NR^3R^4$, $-X^2NR^4S(O)_2R^3$ and $-X^2S(O)_2NR^3R^4$, wherein X^2 is a bond or (C_{1-6})alkylene, R^3 is $-X^2R^5$ wherein X^2 is as defined above and R^5 is aryl containing a total of 6 to 10 ring atoms, heteroaryl containing a total of 5 to 10 ring atoms or unsaturated, partially unsaturated or saturated carbocycloalkyl or heterocycloalkyl each containing a total of 3 to 10 ring atoms, and R^4 at each occurrence independently is hydrogen, (C_{1-6})alkyl or halo-substituted (C_{1-6})alkyl, wherein each ring within A^1 and R^5 that contains from 3 to 8 ring atoms [and] may be substituted with 1 to 3 groups independently selected from (C_{1-6})alkyl, cyano, halo, nitro, halo-substituted (C_{1-6})alkyl, $-X^2OR^4$, $-X^2C(O)R^6$, $-X^2OC(O)R^6$, $-X^2C(O)OR^4$, $-X^2SR^4$, $-X^2S(O)R^6$, $-X^2S(O)_2R^6$, $-X^2NR^4R^4$, $-X^2NR^4C(O)R^6$, $-X^2NR^4C(O)OR^4$, $-X^2C(O)NR^4R^4$, $-X^2NR^4C(O)NR^4R^4$, $-X^2NR^4C(NR^4)NR^4R^4$, $-X^2NR^4S(O)_2R^6$ and $-X^2S(O)_2NR^4R^4$, wherein X^2 and R^4 are as defined above and R^6 is (C_{1-6})alkyl or halo-substituted (C_{1-6})alkyl, and wherein any said carbocycloalkyl and heterocycloalkyl rings within A^1 and R^5 may be substituted further with 1 to 2 groups independently selected from

(C_{1-6})alkylidene, oxo, imino and thioxo, with the provisos that only one of A^1 and R^5 is a fused polycyclic ring system;

A^2 is a monocyclic [or fused bicyclic] ring selected from heteroarylene or unsaturated, partially unsaturated or saturated heterocycloalkylene containing a total of 5 to 11 ring atoms, wherein A^2 may be substituted with a group selected from $-R^8$, $-X^2OR^8$, $-X^2C(O)R^8$, $-X^2OC(O)R^8$, $-X^2C(O)OR^8$, $-X^2SR^8$, $-X^2S(O)R^8$, $-X^2S(O)_2R^8$, $-X^2NR^4R^8$, $-X^2NR^4C(O)R^8$, $-X^2NR^4C(O)OR^8$, $-X^2C(O)NR^4R^8$, $-X^2NR^4C(O)NR^4R^8$, $-X^2NR^4C(NR^4)NR^4R^8$, $-X^2NR^4S(O)_2R^8$ and $-X^2S(O)_2NR^4R^8$, wherein X^2 is a bond or (C_{1-6})alkylene, R^8 is $-X^2R^9$ wherein X^2 is as defined above and R^9 is aryl containing a total of 6 to 10 ring atoms, heteroaryl containing a total of 5 to 10 ring atoms or unsaturated, partially unsaturated or saturated carbocycloalkyl or heterocycloalkyl each containing a total of 3 to 10 ring atoms, and R^4 at each occurrence independently is hydrogen, (C_{1-6})alkyl or halo-substituted (C_{1-6})alkyl, wherein each ring within A^2 and R^8 that contains from 3 to 8 ring atoms [and] may be substituted with 1 to 3 groups independently selected from (C_{1-6})alkyl, cyano, halo, nitro, halo-substituted (C_{1-6})alkyl, $-X^2OR^4$, $-X^2C(O)R^6$, $-X^2OC(O)R^6$, $-X^2C(O)OR^4$, $-X^2SR^4$, $-X^2S(O)R^6$, $-X^2S(O)_2R^6$, $-X^2NR^4R^4$, $-X^2NR^4C(O)R^6$, $-X^2NR^4C(O)OR^4$, $-X^2C(O)NR^4R^4$, $-X^2NR^4C(O)NR^4R^4$, $-X^2NR^4C(NR^4)NR^4R^4$, $-X^2C(O)NR^4X^2C(O)OR^4$, $-X^2NR^4S(O)_2R^6$ and $-X^2S(O)_2NR^4R^4$, wherein X^2 and R^4 are as defined above and R^6 is (C_{1-6})alkyl or halo-substituted (C_{1-6})alkyl, and wherein any said heterocycloalkylene, carbocycloalkyl and heterocycloalkyl rings within A^2 and R^8 may be substituted further with 1 to 2 groups independently selected from (C_{1-6})alkylidene, oxo, imino and thioxo, with the proviso that only one of A^2 and R^8 is a fused polycyclic ring system; and

A^3 is a monocyclic or fused polycyclic ring system selected from aryl containing a total of 6 to 14 ring atoms, heteroaryl containing a total of 5 to 14 ring atoms and unsaturated, partially unsaturated or saturated carbocycloalkyl or heterocycloalkyl each containing a total of 3 to 14 ring atoms, wherein A^3 may be substituted with a group selected from $-R^{9'}$, $-X^2OR^{9'}$, $-X^2C(O)R^{9'}$, $-X^2OC(O)R^{9'}$, $-X^2C(O)OR^{9'}$, $-X^2SR^{9'}$, $-X^2S(O)R^{9'}$, $-X^2S(O)_2R^{9'}$, $-X^2NR^4R^{9'}$, $-X^2NR^4C(O)R^{9'}$, $-X^2NR^4C(O)OR^{9'}$, $-X^2C(O)NR^4R^{9'}$, $-X^2NR^4C(O)NR^4R^{9'}$, $-X^2NR^4C(NR^4)NR^4R^{9'}$, $-X^2NR^4S(O)_2R^{9'}$ and $-X^2S(O)_2NR^4R^{9'}$ [$-R^9$, $-X^2OR^9$, $-X^2C(O)R^9$, $-X^2OC(O)R^9$, $-X^2C(O)OR^9$, $-X^2SR^9$, $-X^2S(O)R^9$, $-X^2S(O)_2R^9$, $-X^2NR^4R^9$, $-X^2NR^4C(O)R^9$, $-X^2NR^4C(O)OR^9$, $-X^2C(O)NR^4R^9$, $-X^2NR^4C(O)NR^4R^9$,

$-X^2NR^4C(NR^4)NR^4R^9$, $-X^2NR^4S(O)_2R^9$ and $-X^2S(O)_2NR^4R^9$], wherein X^2 is a bond or (C_{1-6})alkylene, R9' [R^9] is $-X^2R^{10}$ wherein X^2 is as defined above and R^{10} is aryl containing a total of 6 to 10 ring atoms, heteroaryl containing a total of 5 to 10 ring atoms or unsaturated, partially unsaturated or saturated carbocycloalkyl or heterocycloalkyl each containing a total of 3 to 10 ring atoms, and R^4 at each occurrence independently is hydrogen, (C_{1-6})alkyl or halo-substituted (C_{1-6})alkyl, wherein each ring within A^3 and R^{10} that contains from 3 to 8 ring atoms [and] may be substituted with 1 to 3 groups independently selected from (C_{1-6})alkyl, cyano, halo, nitro, halo-substituted (C_{1-6})alkyl, $-X^2OR^4$, $-X^2C(O)R^6$, $-X^2OC(O)R^6$, $-X^2C(O)OR^4$, $-X^2SR^4$, $-X^2S(O)R^6$, $-X^2S(O)_2R^6$, $-X^2NR^4R^4$, $-X^2NR^4C(O)R^6$, $-X^2NR^4C(O)OR^4$, $-X^2C(O)NR^4R^4$, $-X^2NR^4C(O)NR^4R^4$, $-X^2NR^4C(NR^4)NR^4R^4$, $-X^2NR^4S(O)_2R^6$ and $-X^2S(O)_2NR^4R^4$, wherein X^2 and R^4 are as defined above and R^6 is (C_{1-6})alkyl or halo-substituted (C_{1-6})alkyl, and wherein any said carbocycloalkyl and heterocycloalkyl rings within A^3 and R^{10} may be substituted further with 1 to 2 groups independently selected from (C_{1-6})alkylidene, oxo, imino and thioxo, with the proviso that only one of A^3 and R^{10} is a fused polycyclic ring system; or a *N*-oxide derivative, prodrug derivative, protected derivative, individual stereoisomer or mixture of stereoisomers; or a pharmaceutically acceptable salt thereof.; with the proviso that when said compound is of Formula II(a):



II(a)

then A^3 is other than:

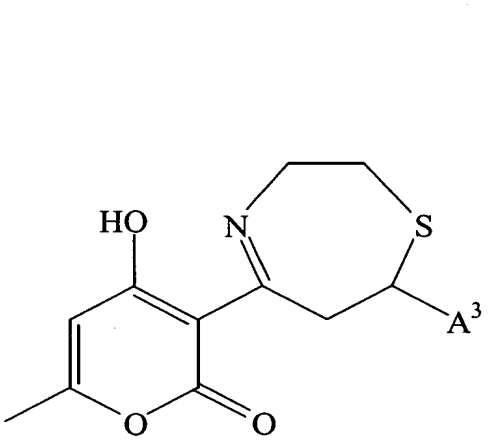
(a) benzo[1,3]dioxolyl;

(b) phenyl which is mono-substituted by bromo, hydroxy, methyl or isopropyl; and

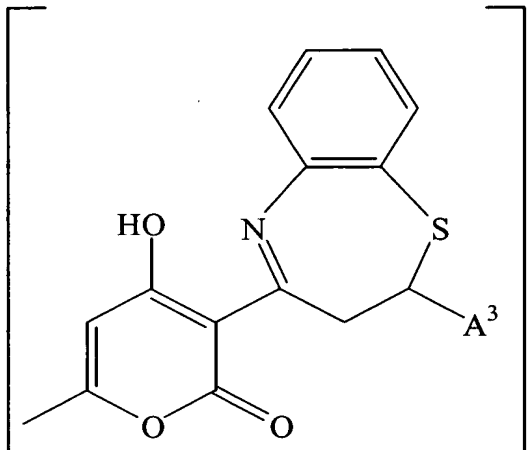
(c) phenyl which is substituted by at least one of Cl and methoxy and not substituted by methylsulfanyl, amino, methylamino and dimethylamino; or

a *N*-oxide derivative, prodrug derivative, protected derivative, individual stereoisomer or mixture of stereoisomers; or a pharmaceutically acceptable salt thereof.

77. The method of claim 76, with the further proviso that when said compound is [selected the group consisting of] Formula II(a) [and II(b)]:



II(a)



II(b)

then A^3 is other than:

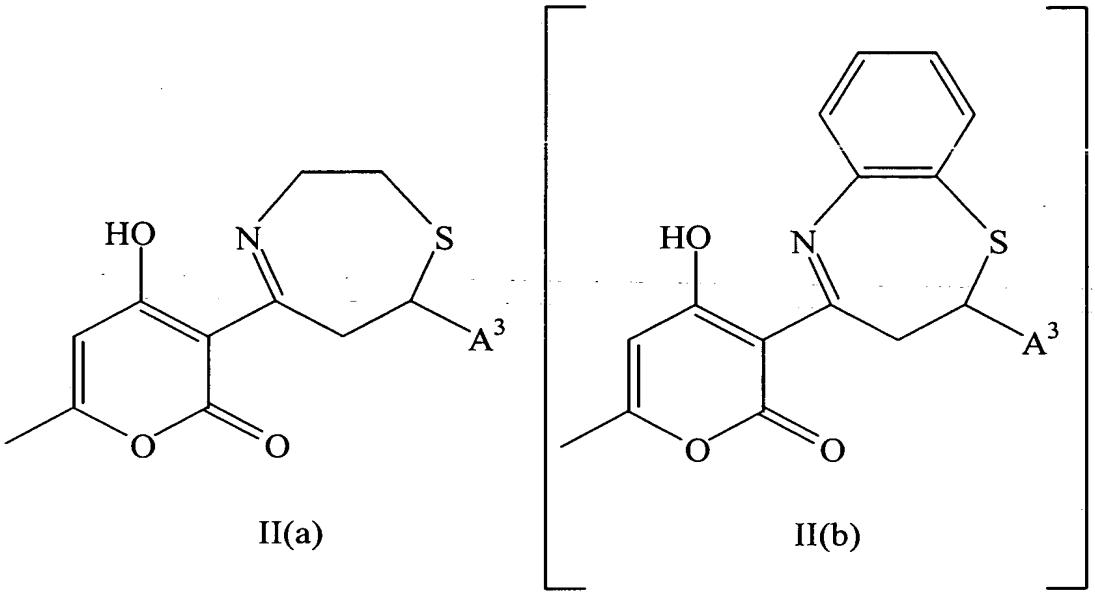
(a) benzo[1,3]dioxolyl;

(b) phenyl which is mono-substituted by bromo, nitro, hydroxy, methyl or isopropyl; and

(c) phenyl which is substituted by at least one of Cl and methoxy and not substituted by methylsulfanyl, amino, methylamino and dimethylamino; or

a *N*-oxide derivative, prodrug derivative, protected derivative, individual stereoisomer or mixture of stereoisomers; or a pharmaceutically acceptable salt thereof.

78. The method of claim 76, with the further proviso that when said compound is [selected the group consisting of] Formula II(a) [and II(b)]:



II(a) II(b)

then A^3 is other than:

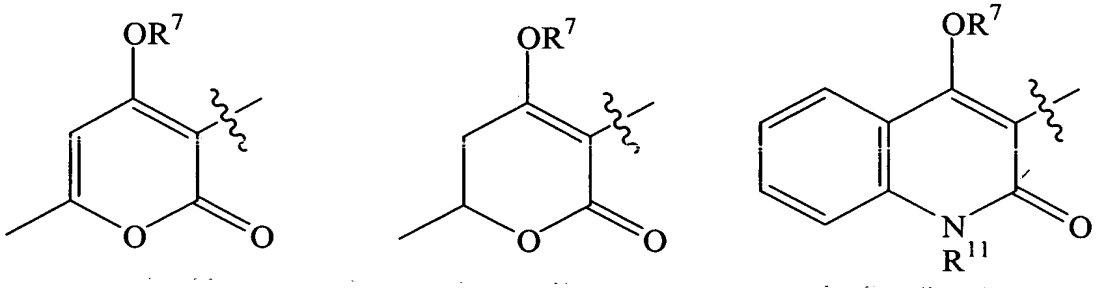
(a) benzo[1,3]dioxolyl;

(b) 2,3-dihydro-benzo[1,4]dioxinyl; and

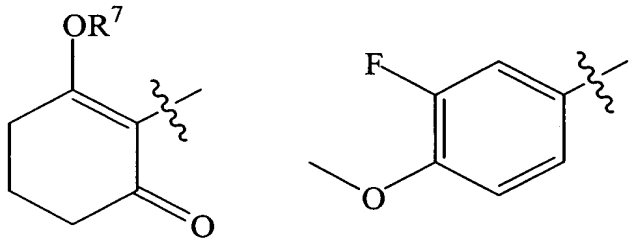
(c) phenyl which is substituted by at least one of bromo, chloro, hydroxy, nitro, methoxy and (C_{1-6}[3])alkyl; or

a *N*-oxide derivative, prodrug derivative, protected derivative, individual stereoisomer or mixture of stereoisomers; or a pharmaceutically acceptable salt thereof.[1.]

79. The method of Claim 76, wherein A^1 of said compound is a group selected from Formulae (a), (b), (c), (d) and (e):



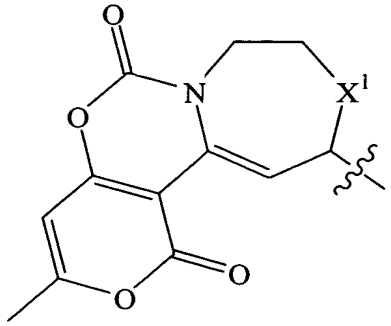
(a) (b) (c)



(d) (e)

in which R^7 is hydrogen or methyl, R^{11} is hydrogen or (C_{1-6})alkyl and the free valance is attached to A^2[, or

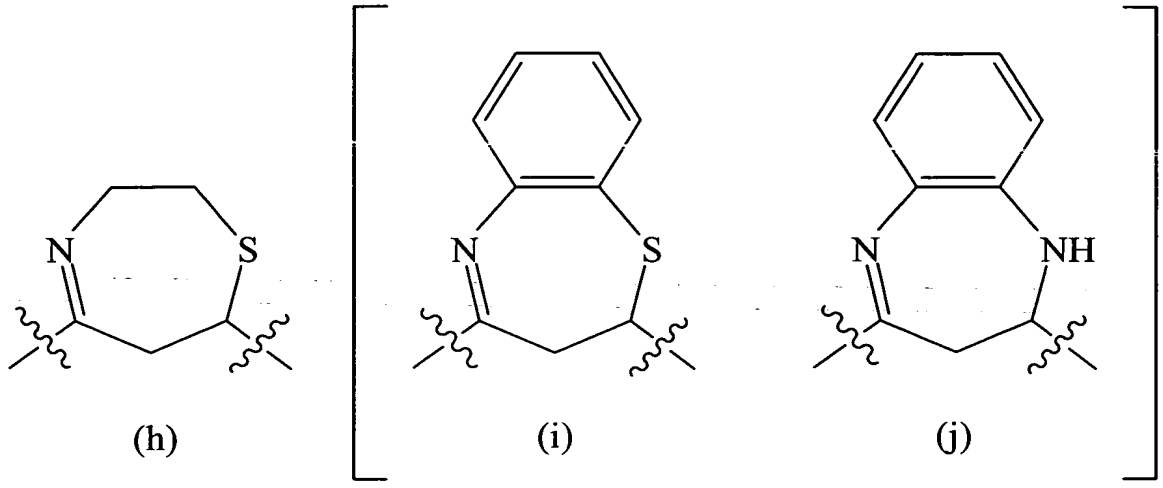
A^2 and A^1 together with R^1 and the atoms to which A^1 and R^1 are attached forms a group of Formula (g):



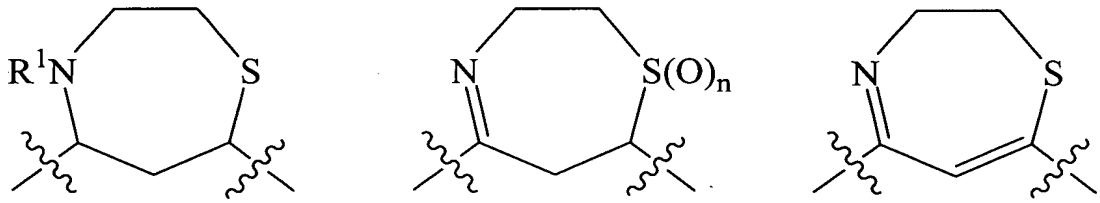
(g)

wherein X^1 is -S- and the free valance is attached to A^3]; and

A^2 of said compound is as defined above or is a group selected from Formulae (h), [(i), (j),] (k), (l) and (m):



(h) (i) (j)



(k) (l) (m)

in which n is 1 or 2 and R^1 is acetyl or trifluoroacetyl; or a *N*-oxide derivative, prodrug derivative, protected derivative, individual stereoisomer or mixture of stereoisomers; or a pharmaceutically acceptable salt thereof.

80. The method of Claim 79, wherein A^3 of said compound is phenyl or heteroaryl containing a total of 5 to 9 ring atoms, wherein A^3 may be substituted with a group selected from $\underline{-R^{9'}, -X^2OR^{9'}, -X^2SR^{9'} \text{ and } -X^2S(O)_2R^{9'}}$ [$-R^9$, $-X^2OR^9$, $-X^2SR^9$ and $-X^2S(O)_2R^9$], wherein $\underline{R^{9'}}$ [R^9] is $-X^2R^{10}$, X^2 is a bond or (C_{1-6})alkylene and R^{10} is phenyl or heteroaryl containing a total of 5 to 6 ring atoms, wherein each ring within A^3 and R^{10} may be substituted with 1 to 3 groups independently selected from (C_{1-6})alkyl, halo, halo-substituted (C_{1-6})alkyl, $-X^2OR^4$, $-X^2SR^4$, $-X^2S(O)_2R^6$ and $-X^2NR^4R^4$, wherein R^4 at each occurrence independently is hydrogen, (C_{1-6})alkyl or halo-substituted (C_{1-6})alkyl and R^6 is (C_{1-6})alkyl or halo-substituted (C_{1-6})alkyl; or a *N*-oxide derivative, prodrug derivative, protected derivative, individual stereoisomer or mixture of stereoisomers; or a pharmaceutically acceptable salt thereof.

82. The method of claim 76, wherein said compound is selected from the group [list] consisting of:

3-[4-acetyl-7-(2,4-dimethoxy-phenyl)-[1,4]thiazepin [thiazepan]-5-yl]-4-hydroxy-6-methyl-pyran-2-one;

3-[7-(2,4-dimethoxy-phenyl)-4-(2,2,2-trifluoro-ethanoyl)-[1,4]thiazepin [thiazepan]-5-yl]-4-hydroxy-6-methyl-pyran-2-one;

1-[7-(2,4-dimethoxy-phenyl)-5-(3-fluoro-4-methoxyphenyl)-[1,4]thiazepin [thizepan]-4-yl]-ethanone;

4-hydroxy-6-methyl-3-[7-(3-phenyl-1*H*-pyrazol-4-yl)-2,3,6,7-tetrahydro-[1,4]thiazepin-5-yl]-pyran-2-one;

3-[7-(5-ethyl-thien-2-yl)-2,3,6,7-tetrahydro-[1,4]thiazepin-5-yl]-4-hydroxy-6-methyl-pyran-2-one;

3-[7-(1-benzyl-1*H*-indol-3-yl)-2,3,6,7-tetrahydro-[1,4]thiazepin-5-yl]-4-hydroxy-6-methyl-pyran-2-one;

4-hydroxy-6-methyl-3[7-(2-trifluoromethylsulfanyl-phenyl)-2,3,6,7-tetrahydro-[1,4]thiazepin-5-yl]-pyran-2-one;

4-hydroxy-6-methyl-3[7-(3-trifluoromethylsulfanyl-phenyl)-2,3,6,7-tetrahydro-[1,4]thiazepin-5-yl]-pyran-2-one;

4-hydroxy-6-methyl-3[7-(4-trifluoromethylsulfanyl-phenyl)-2,3,6,7-tetrahydro-[1,4]thiazepin-5-yl]-pyran-2-one;

4-hydroxy-6-methyl-3-[7-[3-(3-trifluoromethyl-phenoxy)-phenyl]-2,3,6,7-tetrahydro-[1,4]thiazepin-5-yl]-pyran-2-one;

3-[7-[3-(3,4-dichloro-phenoxy)-phenyl]-2,3,6,7-tetrahydro-[1,4]thiazepin-5-yl]-4-hydroxy-6-methyl-pyran-2-one;

3-[7-[3-(3,5-dichloro-phenoxy)-phenyl]-2,3,6,7-tetrahydro-[1,4]thiazepin-5-yl]-4-hydroxy-6-methyl-pyran-2-one;

4-hydroxy-6-methyl-3-{7-[5-(3-trifluoromethyl-phenyl)-furan-2-yl]-2,3,6,7-tetrahydro-[1,4]thiazepin-5-yl}-pyran-2-one;

3-{7-[5-(2-chloro-phenyl)-furan-2-yl]-2,3,6,7-tetrahydro-[1,4]thiazepin-5-yl}-4-hydroxy-6-methyl-pyran-2-one;

3-{7-[5-(3-chloro-phenyl)-furan-2-yl]-2,3,6,7-tetrahydro-[1,4]thiazepin-5-yl}-4-hydroxy-6-methyl-pyran-2-one;

3-{7-[5-(4-chloro-phenyl)-furan-2-yl]-2,3,6,7-tetrahydro-[1,4]thiazepin-5-yl}-4-hydroxy-6-methyl-pyran-2-one;

4-hydroxy-6-methyl-3-{7-[5-(2-chloro-5-trifluoromethyl-phenyl)-furan-2-yl]-2,3,6,7-tetrahydro-[1,4]thiazepin-5-yl}-pyran-2-one;

3-[7-(4-bromo-thien-2-yl)-2,3,6,7-tetrahydro-[1,4]thiazepin-5-yl]-4-hydroxy-6-methyl-pyran-2-one;

3-[7-(5-bromo-thien-2-yl)-2,3,6,7-tetrahydro-[1,4]thiazepin-5-yl]-4-hydroxy-6-methyl-pyran-2-one;

3-[7-(1-benzenesulfonyl-1*H*-pyrrol-2-yl)-2,3,6,7-tetrahydro-[1,4]thiazepin-5-yl]-4-hydroxy-6-methyl-pyran-2-one;

4-hydroxy-6-methyl-3-[7-(3-methyl-thien-2-yl)-2,3,6,7-tetrahydro-[1,4]thiazepin-5-yl]-pyran-2-one;

4-hydroxy-6-methyl-3-[7-(5-methyl-thien-2-yl)-2,3,6,7-tetrahydro-[1,4]thiazepin-5-yl]-pyran-2-one;

4-hydroxy-6-methyl-3-[7-(1-methyl-1*H*-indol-3-yl)-2,3,6,7-tetrahydro-[1,4]thiazepin-5-yl]-pyran-2-one;

3-[7-(3-chloro-2-methyl-5-trifluoromethyl-1*H*-pyrazol-4-yl)-2,3,6,7-tetrahydro-[1,4]thiazepin-5-yl]-4-hydroxy-6-methyl-pyran-2-one;

3-{7-[1-(2,4-difluoro-benzenesulfonyl)-1*H*-pyrrrol-2-yl]-2,3,6,7-tetrahydro-[1,4]thiazepin-5-yl}-4-hydroxy-6-methyl-pyran-2-one;

3-(7-[2,2′]bithienyl-5-yl-2,3,6,7-tetrahydro-[1,4]thiazepin-5-yl)-4-hydroxy-6-methyl-pyran-2-one;

3-{7-[1-(3,5-dichloro-phenyl)-1*H*-pyrrrol-2-yl]-2,3,6,7-tetrahydro-[1,4]thiazepin-5-yl}-4-hydroxy-6-methyl-pyran-2-one;

3-{7-[1-(4-chloro-phenyl)-1*H*-pyrrrol-2-yl]-2,3,6,7-tetrahydro-[1,4]thiazepin-5-yl}-4-hydroxy-6-methyl-pyran-2-one;

3-[7-(5-chloro-1*H*-indol-3-yl)-2,3,6,7-tetrahydro-[1,4]thiazepin-5-yl]-4-hydroxy-6-methyl-pyran-2-one;

[4-hydroxy-6-methyl-3-[7-(6-*p*-tolylsulfanyl-imidazo[2,1-*b*]thiazol-5-yl)-2,3,6,7-tetrahydro-[1,4]thiazepin-5-yl]-pyran-2-one;]

3-[7-(4,5-dibromo-thien-2-yl)-2,3,6,7-tetrahydro-[1,4]thiazepin-5-yl]-4-hydroxy-6-methyl-pyran-2-one;

3-[7-(2-chloro-5-trifluoromethyl-phenyl)-2,3,6,7-tetrahydro-[1,4]thiazepin-5-yl]-4-hydroxy-6-methyl-pyran-2-one;

3-[7-(2,4-dimethoxy-phenyl)-2,3,6,7-tetrahydro-[1,4]thiazepin-5-yl]-4-hydroxy-6-methyl-5,6-dihydro-pyran-2-one;

4-hydroxy-6-methyl-3-[7-(5-methylsulfanyl-thien-2-yl)-2,3,6,7-tetrahydro-[1,4]thiazepin-5-yl]-pyran-2-one;

3-[7-(5-chloro-1-methyl-3-phenyl-1*H*-pyrazol-4-yl)-2,3,6,7-tetrahydro-[1,4]thiazepin-5-yl]-4-hydroxy-6-methyl-pyran-2-one;

[3-[4-(2,4-dimethoxy-phenyl)-4,5-dihydro-3*H*-benzo[*b*][1,4]diazepin-2-yl]-4-hydroxy-6-methyl-pyran-2-one;]

3-[7-(4-dimethylamino-phenyl)-2,3,6,7-tetrahydro-[1,4]thiazepin-5-yl]-4-hydroxy-6-methyl-pyran-2-one;

3-[7-(2,4-dimethoxy-phenyl)-2,3,6,[,]7-tetrahydro-[1,4]thiazepin-5-yl]-4-hydroxy-1*H*-quinolin-2-one;

4-hydroxy-6-methyl-3-[7-(4-trifluoromethoxy-phenyl)-2,3,6,7-tetrahydro-[1,4]thiazepin-5-yl]-pyran-2-one;

3-[7-(bis-trifluoromethyl-phenyl)-2,3,6,7-tetrahydro-[1,4]thiazepin-5-yl]-4-hydroxy-6-methyl-pyran-2-one;

3-[7-(4-dimethylamino-2-methoxy-phenyl)-2,3,6,7-tetrahydro-[1,4]thiazepin-5-yl]-4-hydroxy-6-methyl-pyran-2-one;

[3-hydroxy-2-[2-(2,4-diethoxy-phenyl)-2,3-dihydro-benzo[*b*][1,4]thiazepin-4-yl]-cyclohex-2-enone;]

3-[7-(2,4-dimethoxy-phenyl)-1-oxo-2,3,6,7-tetrahydro-1*H*-1λ^4-[1,4]thiazepin-5-yl]-4-hydroxy-6-methoxy-pyran-2-one;

[10-(2,4-dimethoxy-phenyl)-3-methyl-7,8-dihydro-10*H*-2,5-dioxa-9-thia-6a-aza-cyclohepta[*a*]naphthalene-1,6-dione;]

3-[7-(2,4-dimethoxy-phenyl)-1,1-dioxo-2,3,6,7-tetrahydro-1*H*-1λ^6-[1,4]thiazepin-5-yl]-4-hydroxy-6-methyl-pyran-2-one;

3-[7-(2,4-diethoxy-phenyl)-2,3-dihydro-[1,4]thiazepin-5-yl]-4-hydroxy-6-methyl-pyran-2-one;

3-(7-[2,2′]bithienyl-5-yl-2,3-dihydro-[1,4]thiazepin-5-yl)-4-hydroxy-6-methyl-pyran-2-one;

2-[7-(2,4-diethoxy-phenyl)-2,3-dihydro-[1,4]thiazepin-5-yl]-3-hydroxy-cyclohex-2-enone; and

3-[7-(2,4-diethoxy-phenyl)-2,3-dihydro-[1,4]thiazepin-5-yl]-4-hydroxy-6-methyl-5,6-dihydro-pyran-2-one; or

a *N*-oxide derivative, prodrug derivative, protected derivative, individual stereoisomer or mixture of stereoisomers; or a pharmaceutically acceptable salt thereof.

86. (once amended) The pharmaceutical composition of Claim 55, wherein said cancer therapeutic agent is selected from the group consisting of busulfan, cis-platin, mitomycin C, carboplatin, colchicine, vinblastine, paclitaxel, docetaxel, camptothecin, topotecan, doxorubicin, etoposide, 5-azacytidine, 5-fluorouracil, methotrexate, 5-fluoro-2'-deoxy-uridine, ara-C, hydroxyurea, thioguanine, melphalan, chlorambucil, cyclophosamide, ifosfamide, vincristine, mitoguazone, epirubicin, aclarubicin, bleomycin, imitoxantrone, elliptinium, fludarabine, octreotide, retinoic acid, tamoxifen, HERCEPTIN (trastuzumab), RITUXAN (rituximab) [Herceptin®, Rituxan®] and alanosine.